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PCT/GB 01/02572

12 JUNE 2001

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

REC'D 04 JUL 2001
WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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Signed P. Mahoney

Dated 19 June 2001

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13DEC00 E590969-7 D10057
P01/7700 0.00-0030306.5

Pat nts Form 1/77

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(Rule 16)

The Patent Office

THE PATENT OFFICE
M
13 DEC 2000
NEWPORT

1/77

# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 00218 /GB

2. Pat nt application number *(The Patent Office will fill in this part)* — **0030306.5** — 13 DEC 2000

3. Full name, address and postcode of the or of ach applicant *(underline all surnames)*

Eli Lilly and Company
Lilly Corporate Center
Indianapolis
Indiana 46285
USA

Patents ADP number *(if you know it)* 428904002 IS

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of invention — COMPOUNDS

5. Name of your agent *(if you have one)* — MARTIN ALEXANDER HAY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

13 QUEEN VICTORIA STREET
MACCLESFIELD
CHESHIRE
SK11 6LP

Patents ADP number *(if you know it)* ~~4345573001~~ 7710858001 IS

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body*
*See note (d))*

No

**Patents Form 1/77**

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| | |
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| Continuation sheets of this form | 0 |
| Description | 79 ✓ |
| Claim(s) | 14 ✓ |
| Abstract | 1 ✓ |
| Drawing(s) | 0 |

10. If you are also filing any of the following, state how many against each item.

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| Priority documents | 0 |
| Translations of priority documents | 0 |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | 0 |
| Request for preliminary examination and search *(Patents Form 9/77)* | 0 |
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| Any other documents *(please specify)* | 0 |

11. I/We request the grant of a patent on the basis of this application

Signature Martin A Hay Date: 12 Dec 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

MARTIN A. HAY 01625 500057

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# COMPOUNDS

This invention relates to compounds which are inhibitors of serine proteases and to pharmaceutical compositions thereof and their use in the treatment of the human or animal body.

The serine proteases are a group of proteolytic enzymes which have a common catalytic mechanism characterized by a particularly reactive Ser residue. Examples of serine proteases include trypsin, tryptase, chymotrypsin, elastase, thrombin, plasmin, kallikrein, Complement C1, acrosomal protease, lysosomal protease, cocoonase, α-lytic protease, protease A, protease B, serine carboxypeptidase II, subtilisin, urokinase, Factor VIIa, Factor IXa, and Factor Xa. The serine proteases have been investigated extensively over a period of several decades and the therapeutic value of inhibitors of serine proteases is well understood.

Serine protease inhibitors play a central role in the regulation of a wide variety of physiological process including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. It is well known that these compounds inhibit a variety of circulating proteases as well as proteases that are activated or released in tissue. It is also becoming clear that serine protease inhibitors inhibit critical cellular processes, such as adhesion, migration, free radical production and apoptosis. In addition, animal experiments indicate that intravenously administered serine protease inhibitors, variants or cells expressing serine protease inhibitors, provide a protective effect against tissue damage.

Serine protease inhibitors have also been predicted to have potential beneficial uses in the treatment of disease in a wide variety of clinical areas such as oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious disease.

In particular serine protease inhibitors may be beneficial in the treatment of thrombotic diseases, asthma, emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenosis, atheroma, trauma, shock and reperfusion injury.

Thus for example an inhibitor of Factor Xa has value as a therapeutic agent as an anticoagulant, e.g. in the treatment and prevention of thrombotic disorders. The use of a Factor Xa inhibitor as an anticoagulant is desirable in view of the selectivity of its effect. Many clinically approved anticoagulants have been associated with adverse events owing to the non-specific nature of their effects on the coagulation cascade.

Also, there are well-known associations of α1 protease inhibitor deficiency with emphysema and cirrhosis and C1 esterase inhibitor deficiency with angioedema.

It has now been found that certain aromatic compounds are particularly effective as inhibitors of serine proteases, especially proteases with negatively charged P1 specificity pockets, and most especially the serine protease Factor Xa. The Factor Xa inhibitors of this invention are potentially useful for the prophylaxis or treatment of thrombotic disorders such as amongst others venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction, and cerebral thrombosis. They potentially have benefit in the treatment of acute vessel closure associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients.

Factor Xa inhibitors of this invention may, with benefit, form part of a combination therapy with an anticoagulant with a different mode of action or with a thrombolytic agent.

It has been reported in WO99/11658 and WO99/11657 that certain benzamidine and aminoisoquinoline derivatives carrying a bulky lipophilic side chain are excellent inhibitors of serine proteases. Unfortunately, it has since been found that benzamidine compounds of WO 99/11658 in general demonstrate poor oral bioavailability.

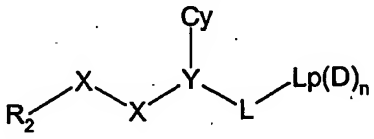
Surprisingly, it has now been found that certain other aromatic compounds also show inhibitory activity against serine proteases, in particular Factor Xa, despite the lack of

the amidino or 1-aminoisoquinoline functionality previously believed to be crucial for activity as a factor Xa inhibitor. Many of these compounds also possess other structural features that further distinguish them from the compounds of WO99/11658 and WO99/11657.

Where compounds of the invention have been tested, they have generally demonstrated superior oral bioavailability in comparison with benzamidines disclosed in WO 99/11658. Also, it has been found that the compounds of the invention perform excellently in the prothrombin time assay (PT) when compared to aminoisoquinolines of similar factor Xa activity and structure. The PT assay is a coagulation assay and it is widely accepted that direct acting Factor Xa inhibitors which perform well in the PT assay are more likely to be good antithrombotics.

In WO99/09053 certain 2-aminobenzamide compounds are disclosed as potential motilin receptor antagonists and in US 3268513 similar 2-aminobenzamide compounds are suggested as potential antibacterial agents. However, the novel compounds of the present invention have not before been suggested as potential serine protease inhibitors.

Thus viewed from an one aspect the invention provides a serine protease inhibitor compound of formula (I)




(I)

wherein:

$R_2$ is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or $R_1$, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy,

haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that $R_2$ cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, $CR_{1a}$, $C(R_{1a})_2$ or $NR_{1a}$ group, at least one X being C, CO, $CR_{1a}$ or $C(R_{1a})_2$;

each $R_{1a}$ independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

$R_1$ is as defined for $R_{1a}$, provided that $R_1$ is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a $CR_{1b}$ group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups $R_{3a}$ or phenyl optionally substituted by $R_{3a}$ or $R_{3i}X_i$;

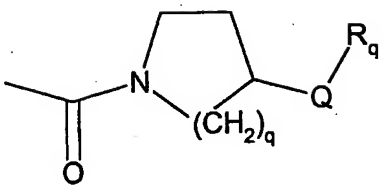
each $R_{3a}$ independently is $R_{1c}$, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein $X^3$ is O or S; and $R^{11}$ and $R^{12}$ are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

$X_i$ is a bond, O, NH or $CH_2$;

$R_{3i}$ is phenyl pyridyl or pyrimidinyl optionally substituted by $R_{3a}$;

$R_{1b}$, $R_{1c}$ and $R_{1j}$ are as defined for $R_{1a}$; and

$-L-Lp(D)_n$ is



q is 1 or 2;

Q is methylene; and $R_q$ is $NR_aR_b$ in which each of $R_a$ and $R_b$ independently is hydrogen or $C_{1-3}$alkyl; or one of $R_a$ and $R_b$ is hydrogen or methyl and the other of $R_a$ and $R_b$ is (3-6C)cycloalkyl, pyrid-4-yl, $-CH_2-R_c$ or $-CH_2-R_d$ in which $R_c$ is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, $SO_2NH_2$, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which $R_d$ is isopropyl or cyclopentyl, or $NR_aR_b$ is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino may be optionally substituted on a ring carbon atom by hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl (provided that the amino, hydroxy or alkoxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring oxygen, sulfur or nitrogen atom) and in which the piperazino or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position];

or a physiologically-tolerable salt thereof, e.g. a halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

In the compounds of the invention, where the alpha atom is carbon it preferably has the conformation that would result from construction from a D-α-aminoacid $NH_2-CR_{1b}(Cy)-COOH$ where the $NH_2$ represents part of X-X. Likewise the fourth substituent $R_{1b}$ at an alpha carbon is preferably a methyl or hydroxymethyl group or hydrogen.

In the compounds of the invention, unless otherwise indicated, aryl groups preferably contain 5 to 10 ring atoms optionally including 1, 2 or 3 heteroatoms selected from O, N and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. $C_{1-6}$ or $C_{1-3}$; cyclic groups preferably have ring sizes of 3 to 8 atoms; and fused multicyclic groups preferably contain 8 to 16 ring atoms.

Examples of particular values for $R_{1a}$ are: hydrogen, methyl or ethyl. $R_{1a}$ is preferably a hydrogen atom.

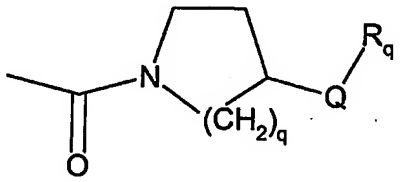
The linker group from the $R_2$ group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -CONR$_{1a}$-, -NH-CO-, -NH-$CH_2$-, -$CH_2$-NH-, -$CH_2$O-, -O$CH_2$-, -COO-, -OC=O- and -$CH_2CH_2$-. Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as $CH_2$ or CO, preferably CO. Thus a particularly preferred linker X-X is -CONH-. In an alternative embodiment the linker is preferably a -O$CH_2$- group.

Examples of particular values for $R_{1b}$ are: hydrogen, (1-4C)alkyl, such as methyl or hydroxy(1-4C)alkyl, such as hydroxymethyl. $R_{1b}$ is preferably a hydrogen atom.

The alpha atom (Y) is preferably a CH or C($CH_3$) group, especially CH.

In the group -L-Lp(D)$_n$, preferably the azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or tetrahydro-1,4-diazepino in $NR_aR_b$ is optionally substituted on a ring carbon atom by methyl, hydroxy or hydroxymethyl.

A preferred sub-group of compounds of formula I is that in which wherein -L-Lp(D)$_n$ is of the formula:




wherein:

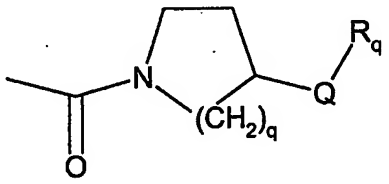
q is 1 or 2;

Q is methylene; and $R_q$ is $NR_aR_b$ in which each of $R_a$ and $R_b$

independently is hydrogen or $C_{1-3}$alkyl; or one of $R_a$ and $R_b$ is hydrogen or methyl and the other of $R_a$ and $R_b$ is $-CH_2-R_c$ or $-CH_2-R_d$ in which $R_c$ is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, $SO_2NH_2$, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which $R_d$ is isopropyl or cyclopentyl, or $NR_aR_b$ is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino may be a 3,4-didehydro deriviative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 3- or 4-position.

q is preferably 2.

Preferably $-L-Lp(D)_n$ is of the formula:




wherein:

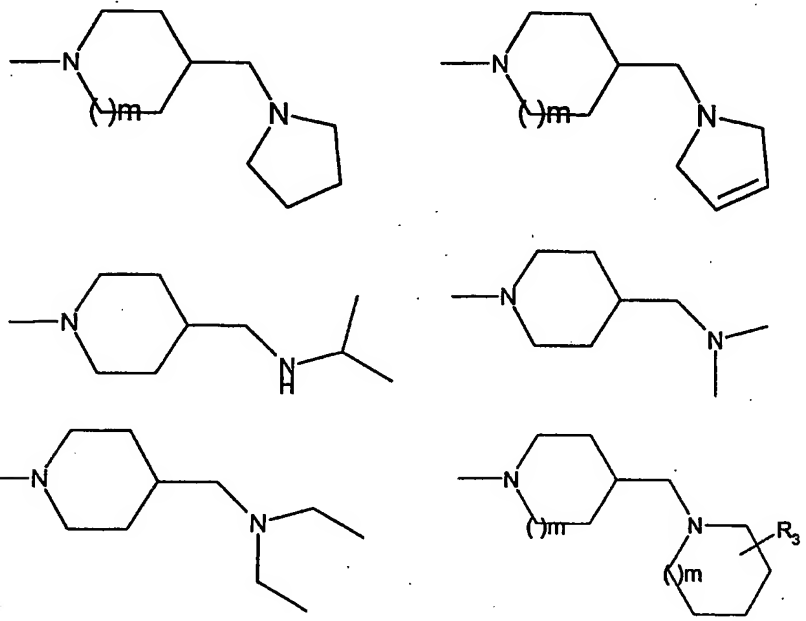
q is 1 or 2;

Q is methylene; and $R_q$ is $NR_aR_b$ in which each of $R_a$ and $R_b$ independently is hydrogen or $C_{1-3}$alkyl; or one of $R_a$ and $R_b$ is hydrogen and the other is (3-6C)cycloalkyl or pyrid-4-yl; or $NR_aR_b$ is azetidino, pyrrolidino, piperidino or piperazino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino, pyrrolidino, piperidino or piperazino may be optionally substituted on a ring carbon atom by methyl, hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

Preferably $R_q$ is $NR_aR_b$ in which $R_a$ is hydrogen or $C_{1-3}$alkyl and $R_b$ is $C_{1-3}$alkyl; or $R_a$ is hydrogen and $R_b$ is (3-6C)cycloalkyl or pyrid-4-yl; or $NR_aR_b$ is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino [in which a pyrrolidino, piperidino or piperazino may be optionally substituted on a ring carbon atom by hydroxy

or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

Most preferably, the group L-Lp(D)$_n$ is selected from

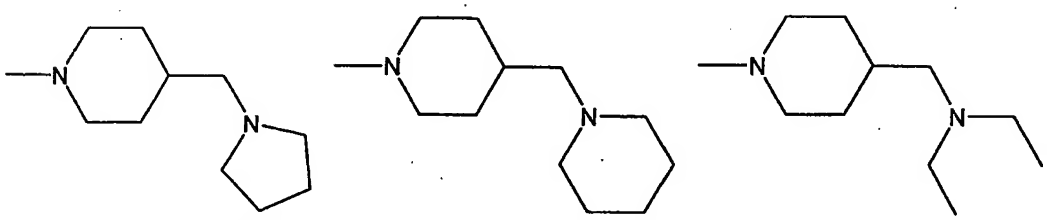


wherein:

m represents 0 or 1;

and when $R_3$ is present as a substituent on a saturated ring, it is selected from hydrogen, hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl and ethoxycarbonyl.

For example specific groups of formula L-Lp(D)$_n$ include



Cy is preferably an optionally $R_{3a}$ substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinoloyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group

substituted by $R_{3i}X_i$ in which $X_i$ is a bond, O, NH or $CH_2$ and $R_{3i}$ is phenyl, pyridyl or pyrimidinyl optionally substituted by $R_{3a}$.

The cyclic group attached to the alpha carbon may thus be an optionally $R_{3a}$ substituted phenyl, pyridyl (such as pyrid-2-yl, pyrid-3-yl or pyrid-4-yl), thienyl (such as thien-2-yl or thien-3-yl), thiazolyl (such as thiazol-2-yl, thiazol-4-yl or thiazol-5-yl), naphthyl (such as naphth-1-yl), piperidinyl (such as piperidin-4-yl) or cycloalkyl, such as a cyclohexyl group.

Examples of values for Cy when it represents phenyl substituted by $R_{3i}X_i$ are 3-(2-pyridyl)phenyl, 3-(3-pyridylphenyl and 3-(4-pyridylphenyl).

Examples of particular values for $R_{3a}$ are:-

hydrogen;

hydroxyl;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;

for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: hydroxymethyl or carboxy;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;

for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;

for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$ or $CH_2CONH_2$;

for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as acetylamino;

for alkoxycarbonylamino: methoxycarbonylaminno, ethoxycarbonylamino or t-butoxycarbonylamino;

amino;

for halo: fluoro, chloro or bromo;

cyano;

nitro;
thiol;
for alkylthio: methylthio;
for alkylsulphonyl: methylsulphonyl or ethylsulphonyl;
for alkylsulphenyl: methylsulphenyl;
for alkylsulphonamido: methylsulphonylamido or ethylsulphonylamido;
for alkylaminosulphonyl: methylaminosulphonyl or ethylaminosulphonyl;
aminosulphonyl;
for haloalkoxy: trifluoromethoxy;
for haloalkyl: trifluoromethyl;
for a group of formula $-C(X^3)N(R^{11})R^{12}$: pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl or morpholin-1-ylcarbonyl; and
$-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy.

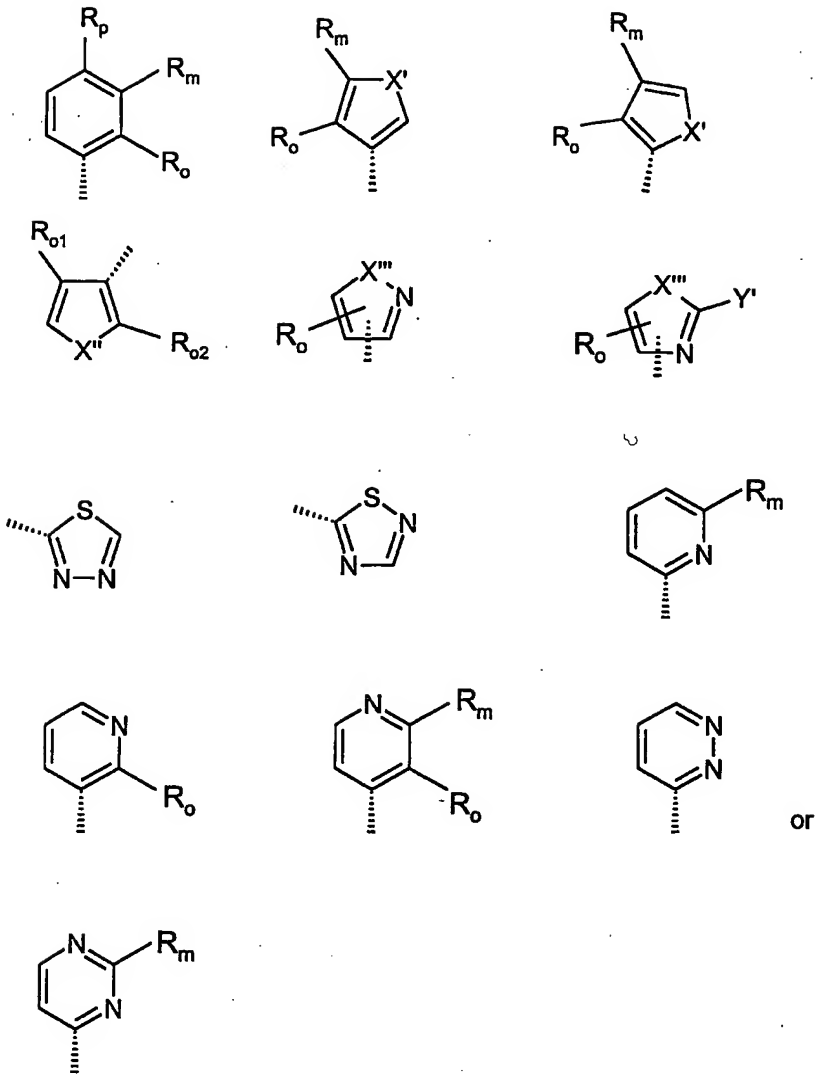
Examples of particular values for $R_{1c}$ are:
hydrogen;
hydroxyl;
for alkoxy: methoxy or ethoxy;
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;
for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycabonyl or ethoxycarbonyl;
for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;
for alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino;
for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as acetylamino; and
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$ or $CH_2CONH_2$.

Preferably $R_{3a}$ is hydrogen, hydroxyl, methoxy, methyl, amino, fluoro, chloro, ethylsulphonylamino, amido or methylaminocarbonyl.

Examples of values for $R_{31}$ are phenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl pyrimid-2-yl and pyrimid-6-yl.

Examples of particular values for Cy are phenyl, 4-aminophenyl, 4-amidophenyl, 4-(N-methyl)amidophenyl, 4-(N,N-dimethyl)amidophenyl, 2-chlorophenyl, 2-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-hydroxphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-carboxyphenyl, 3-ethylsulphonylaminophenyl, thien-2-yl, thien-3-yl, thiazol-4-yl, thiazol-5-yl, 2-methylthiazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, cyclohexyl and naphth-1-yl.

Particular mention is made of the following values for Cy:



or

wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

$R_o$ is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

$R_m$ is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein $X^3$ is O or S, and $R^{11}$ and $R^{12}$ are

independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group); $R_p$ is selected from hydrogen and fluoro; or $R_o$ and $R_m$ or $R_m$ and $R_p$ form an -OCH2O- group; or $R_o$ and $R_m$ together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and

one of $R_{o1}$ and $R_{o2}$ is hydrogen and the other is $R_o$.

wherein Cy is selected from phenyl (optionally substituted by ethyl, prop-2-yl, phenoxy, hydroxy, ethoxy, benzyloxy, prop-2-yloxy, nitro, amino, acetylamino, methylsufonylamino, dimethylamino, chloro, methoxy, trifluoromethyl, methylthio, methylsulfonyl, tert-butylthio, tert-butylsulfonyl, aminosulfonyl or carbamoyl), pyridyl, thienyl, furanyl, imidazolyl, thiazolyl (optionally substituted by amino or methyl), napththyl, isoquinolinyl and quinolinyl.

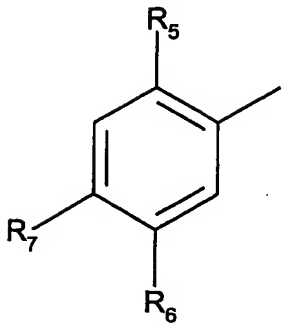
Preferably Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

More preferably Cy is selected from phenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5yl and quinolin-4-yl.

A value for Cy of particular interest is phenyl.

Referring to the group $R_2$, examples of a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom are phenyl; pyrrolyl, such as 2-pyrrolyl; pyridyl, such as 3-pyridyl; pyrazinyl, such as 2-pyrazinyl; furyl, such as 2-furyl; and thienyl, such as 2-thienyl or 3-thienyl. Preferably the ring is interrupted (i.e. a carbon atom is replaced) by at most one heteroatom. More preferably the ring is phenyl, 2-thienyl or 2-pyrrolyl. Most preferably, the ring is phenyl.

When the ring is phenyl, the group $R_2$ may be a group of formula




in which $R_5$ is amino, hydroxy or hydrogen, and $R_6$ and $R_7$ which may be the same or different represent halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or $R_1$ or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered heterocyclic ring, which may itself be substituted by $R_{1j}$, amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl, haloalkoxy.

When the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring, examples of the resultant bicyclic ring are naphthyl, such as 2-naphthyl; benzimidazolyl, such as benzimidazol-5-yl or benzimidazol-6-yl; isoquinolinyl, such as isoquinolin-7-yl; indolyl, such as indol-2-yl, indol-5-yl or indol-6-yl; indazolyl, such as indazol-5-yl; indazol-6-yl; 3,4-methylenedioxyphenyl; dihydroindolyl, such as 2,3-dihydroindol-6-yl; benzothiazolyl, such as benzothiazol-2-yl or benzothiazol-6-yl; benzo[b]thiophenyl, such as benzo[b]thiophen-2-yl; benzofuryl, such as benzofur-2-yl; imidazo[1,2-a]pyrimidinyl, such as imidazo[1,2-a]pyrimidin-2-yl; tetrahydroimidazo[1,2-a]pyrimidinyl, such as tetrahydroimidazo[1,2-a]pyrimidin-2-yl; and benzisoxazolyl, such as benzisoxazol-5-yl.

Preferably $R_2$ is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl, optionally substituted as defined hereinabove.

$R_2$ preferably represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or $R_1$, and optionally substituted at the 6 position by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(ii) naphth-2-yl optionally substituted at the 6 or 7 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$ and optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$;

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_1$;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_1$;

(ix) pyrid-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_1$;

(x) pyrid-3-yl optionally substituted at the 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_1$;

(xi) benzofur-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6

position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by alkyl and optionally substituted at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$;

(xiii) indol-6-yl substituted at the 5 position by amino, hydroxy, halo (such as fluoro or chloro), alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio and optionally substituted at the 3 position by halo (such as chloro), haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$; or

(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$.

Examples of particular values for substituents that may be present on $R_2$ are:

for halo: fluoro, chloro, bromo or iodo;

nitro;

thiol;

for haloalkoxy: difluoromethoxy or trifluoromethoxy;

hydrazido;

for alkylhydrazido: methylhydrazido;

amino;

cyano;

for haloalkyl: trifluoromethyl;

for alkylthio: methylthio;

for alkenyl: vinyl;

for alkynyl: ethynyl;

for acylamino: acetylamino;

carboxy;

for acyloxy: acetoxy;

hydroxy;

for alkyl: methyl or ethyl;

amido ($CONH_2$);

for aminoalkyl: aminomethyl; and

for alkoxy: methoxy or ethoxy.

Preferably $R_2$ is optionally substituted by 1 or 2 substituents selected from fluoro, chloro, amino, methyl, ethyl and methoxy.

Examples of particular values for $R_1$ are:
hydrogen;
hydroxy;
for alkoxy: methoxy or ethoxy;
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, alkylaminoalkyl, such as dimethylaminomethyl, or alkanoyl, such as acetyl;
for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycarbonyl;
for alkylaminocarbonyl: methylaminocarbonyl;
for alkylamino: methylamino, ethylamino or dimethylamino;
for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amido ($CONH_2$) or amidomethyl.

Examples of particular values for $R_{1j}$ are:
hydrogen;
hydroxy;
for alkoxy: methoxy or ethoxy;
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkanoyl, such as acetyl;
for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycarbonyl;
for alkylamino: methylamino, ethylamino or dimethylamino;
for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amido ($CONH_2$) or amidomethyl.

More preferably $R_2$ represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by fluoro, chloro, bromo, iodo, nitro, difluoromethoxy, trifluoromethoxy, amino, cyano, trifluoromethyl, methylthio, vinyl, carboxy, acetoxy, $MeSO_2$-, hydroxy, methoxy, ethoxy, methyl, methoxycarbonyl, methylamino, ethylamino or amido, and optionally substituted at the 6 position by amino, hydroxy, fluoro, methoxycarbonyl, cyano or aminomethyl (preferably phenyl substituted in the 4 position by chloro, amino, vinyl, methylamino, methyl or methoxy, optionally at the 3 position with amino or hydroxy, and optionally at the 6 position with amino or hydroxy);

(ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 position by amino or hydroxy;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy (preferably indol-6-yl optionally substituted at the 3 position by chloro, bromo, methyl or methoxy);

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl substituted at the 5 position by methyl;

(ix) pyrid-2-yl optionally substituted at the 6 position by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

(xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

(xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy.

Examples of particular values for $R_2$ are:

(i) phenyl, 2-aminophenyl, 3-aminophenyl, 2-amino-3-fluorophenyl, 2-amino-4-fluorophenyl, 2-amino-4-chlorophenyl, 2-amino-3-bromophenyl, 2-amino-3-nitrophenyl, 2-amino-4-nitrophenyl, 3,4-dimethoxy-5-aminophenyl, 2-amino-4-methylphenyl, 2-amino-3-methylphenyl, 2-amino-3-methoxyphenyl, 3,4-diaminophenyl, 3,5-diaminophenyl, 3-amino-4-fluorophenyl, 3-amino-4-chlorophenyl, 3-amino-4-bromophenyl, 3-amino-4-hydroxyphenyl, 3-amino-4-carboxymethylphenyl, 3-amino-4-methylphenyl, 3-amino-4-methoxyphenyl, 2-fluorophenyl, 4-fluoro-3-cyanophenyl, 3-chlorophenyl, 3-chloro-4-hydroxphenyl, 3-chloro-5-hydroxyphenyl, 4-chlorophenyl, 4-chloro-2-hydroxyphenyl, 4-chloro-3-hydroxyphenyl, 4-chloro-3-methylphenyl, 4-chloro-3-methoxyphenyl, 4-bromophenyl, 4-bromo-3-methylphenyl, 4-iodophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-cyano-5-aminophenyl, 2-hydroxphenyl, 2-hydroxy-4-methoxyphenyl, 3-hydroxphenyl, 3-hydroxy-4-methylphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 3-hydroxy-4-methoxyphenyl, 4-difluoromethoxyphenyl, 4-trifluoromethoxphenyl, 4-trifluoromethylphenyl, 4-methylthiophenyl, 4-methoxycarbonylphenyl, 4-acetoxyphenyl, 4-methanesulfonylphenyl, 3-methylphenyl, 3-methyl-5-aminophenyl, 4-methylphenyl, 4-vinylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-methoxy-3-chlorophenyl, 4-methoxy-3-methylphenyl, 3-methylaminophenyl, 4-methylaminophenyl, 4-ethylaminophenyl or 2-aminomethylphenyl;

(ii) naphth-2-yl, 3-aminonaphth-2-yl, 3-hydroxynaphth-2-yl or 6-hydroxynaphth-2-yl;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, 3-chloroindol-6-yl, 3-bromoindol-6-yl, 3-methylindol-6-yl, 3-methoxyindol-6-yl, indazol-5-yl, 3-aminoindazol-5-yl, indazol-6-yl, benzothiazol-6-yl, 3-aminobenzisoxazol-5-yl;

(iv) benzimidazol-5-yl, 2-aminobenzimidazol-5-yl, or benzothiazol-6-yl;

(v) thien-2-yl, 5-methylthien-2-yl, 5-methylthio-thien-2-yl, 5-acetylthien-2-yl or thien-3-yl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) 5-methylpyrazol-2-yl;

(ix) 5-chloropyrid-2-yl;

(x) pyrid-3-yl, 6-chloropyrid-3-yl;

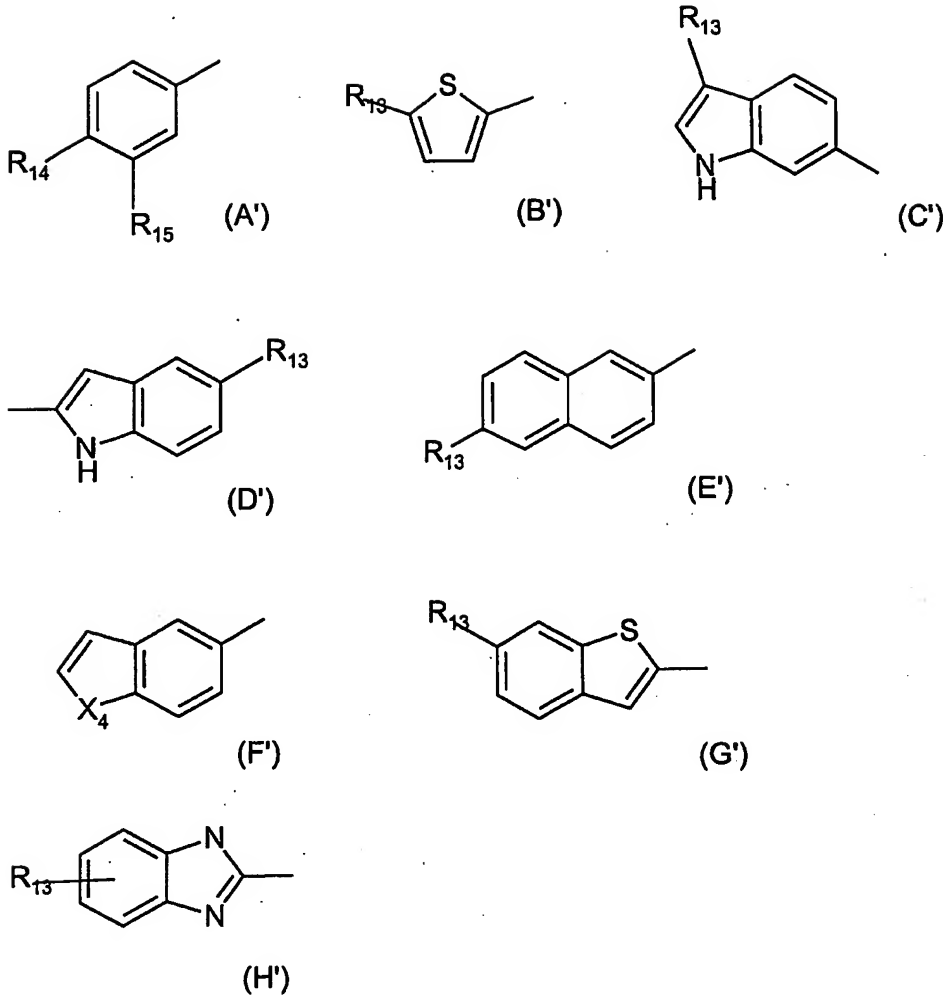
(xi) benzofur-2-yl, 5-chlorobenzofur-2-yl, 3-methylbenzofur-2-yl, 5-methylbenzofur-2-yl, 6-methoxybenzofur-2-yl;

(xii) indol-2-yl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-methylindol-2-yl, 5-methoxindol-2-yl, 6-methoxyindol-2-yl and 1-methyl-indol-2-yl;

(xiii) 5-fluoroindol-6-yl; or

(xiv) benzo[b]thiophen-2-yl, 5-chloro- benzo[b]thiophen-2-yl or 6-chlorobenzo[b]thiophen-2-yl.

$R_2$ may, for example, be selected from one of the formula (A') to (H'):




wherein $X_4$ is O or S, $R_{13}$ is selected from hydrogen, chloro or methyl and $R_{14}$ is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and $R_{15}$ is selected from hydrogen, methyl, fluoro, chloro and amino.

Preferably $R_2$ is of the formula (A') (wherein $R_{14}$ is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and $R_{15}$ is selected from hydrogen, methyl, fluoro, chloro and amino) or of the formula (B') (wherein $R_{13}$ is chloro) or of the formula (C') (wherein $R_{13}$ is selected from hydrogen, methyl and chloro) or of the formula (D') (wherein $R_{13}$ is selected from hydrogen and chloro) or of the formula (E') (wherein $R_{13}$ is hydrogen) or of the formula (G') (wherein $R_{13}$ is chloro).

More preferably $R_2$ is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

$R_2$ is preferably of the formula (A') and $R_{14}$ and $R_{15}$ are as defined hereinabove. More preferably $R_2$ is of the formula (A') and $R_{14}$ is methoxy and $R_{15}$ is hydrogen.

It is preferred that at least one of $R_6$ and $R_7$ be other than hydrogen and that $R_6$, if present, is preferably a substituent containing one or more polar hydrogens such as hydroxy, amino, alkylamino, alkylaminoalkyl, aminocarbonyl, alkylaminocarbonyl, hydrazo and alkylhydrazo; alternatively $R_6$ and $R_7$ are joined together in the formation of a naphthyl or indolyl or azaindolyl or diazaindolyl group.

It is especially preferred that $R_6$ be amino and $R_7$ be chloro, bromo, methyl, methoxy or vinyl; or that $R_6$ and $R_7$ taken together form an indolyl ring with the NH at the 6-position or taken together form a naphthyl ring.

The compounds of the invention may be prepared by conventional chemical synthetic routes or by routes as illustrated by the following examples.

The compounds of the formula (I) may be prepared by forming the -X-X- bond from appropriate intermediates. For example, when -X-X- is -CONH- or -CO-$NR_{1a}$-, by reacting a compound of the formula (10): $H_2N$-Y-(Cy)-L-Lp(D)$_n$ with a compound of the formula $R_2$-COOH, under conditions known for the formation of an amide bond. The reaction is conveniently carried out in the presence of a benzotriazole-based reagent such as 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole, in an inert organic solvent such as dimethylformamide and/or methylene chloride . The reaction mixture is usually taken to 0°C and then a dehydrating agent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide added. Other suitable reagents and solvents are known in the art.

Compounds wherein -X-X- is -NHCO- or -$NHCH_2$- may be formed from the appropriate intermediates using reaction conditions for the formation of an amide bond as described above and if necessary subsequent reduction of the resulting amide bond.

Compounds of the formula (I) wherein -X-X- is of the formula -$CH_2NH$- may be prepared by reducing the corresponding

compound of the formula (I) wherein -X-X- is -CONH-, or by reaction of a compound of formula (10)

$$H_2N\text{-}Y(Cy)\text{-}L\text{-}Lp(D)_n$$

with a comound of the formula $R_2CHO$ and reducing the intermediate of formula (I) where X-X is C=N- with, for example, sodium cyanoborohydride.

When -X-X- is -CH=CH-, the compounds of the formula (I) may be prepared using the Wittig or Horner-Emmous reactions. The corresponding compound in which -X-X- is $-CH_2CH_2-$ can be formed by reduction of the -CH=CH- group, for example with hydrogen over a palladium-on-carbon catalyst.

An -X-X- bond of the formula -COO- or -OC(O)- may be formed by reacting the appropriate hydroxy and activated carboxylic acid (e.g. acid chloride or reactive ester) intermediates under conditions known for ester bond formation. Alternatively, a hydroxy and a carboxylic acid intermediate could be reacted together in the presence of diethylazodicarboxylate/triphenylphosphine.

An -X-X- bond of the formula $-CH_2O-$ or $-OCH_2-$ may be formed by reacting the appropriate hydroxy intermediate with the appropriate alkyl halide in the presence of a base. Conditions for the formation of an ether bond are known in the art.

These reactions can also be used to form intermediates, which contain one of the above -X-X- bonds.

Compounds of the formula (I) may also be prepared by introducing the Lp(D)n group into a compound of the formula (11):

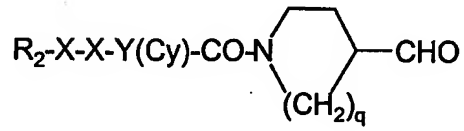
$$R^2\text{-}X\text{-}X\text{-}Y(Cy)\text{-}COOH$$

Reactive groups in $Lp(D)_n$, which could cause side-reactions can of course be protected. The reaction between the compound (11) and $Lp(D)_n$ is conveniently carried out in an inert organic solvent, in the presence of an organic base such as an amine (e.g. ethyldiisopropyamine), additionally in the presence of a reagent such as diethylcyanophosphonate.

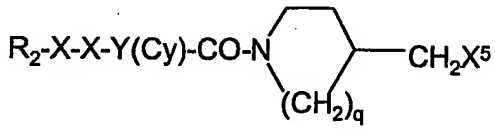
Intermediates which already contain the $Lp(D)_n$ group may be prepared from the appropriate carboxy compound using

similar reaction conditions to those described above.

Compounds of the formula (I) can also be prepared by reacting a compound of the formula (12):



or (13):



(wherein $X^5$ is a leaving group such as tosyloxy, mesyloxy or halo) with a compound of formula $HNR_aR_b$. The reaction between the compound of formula (13) and $HNR_aR_b$ may be carried out using conditions similar to those described in Examples 1 to 5. The reaction between the compound of formula (12) and $HNR_aR_b$ may be carried out in an inert organic solvent such as THF, in the presence of an inorganic base such as potassium carbonate, and preferably in the presence of sodium iodide. The reaction usually takes place at or near reflux of THF.

Intermediates containing the $Lp(D)_n$ group can also be formed using these reactions from appropriate intermediates, although normally the introduction of the $HNR_aR_b$ group is the last step in the synthesis.

Hence the present invention also provides a process for the preparation of a compound of formula (I) comprising:

a) when -X-X is -CONH-, reacting a compound of formula (10) with a compound of formula $R_2$-COOH, under amide bond-forming conditions;

b) reacting a compound of formula (11) with a compound of formula $Lp(D)_n$ under amide bond-forming conditions; or

c) reacting a compound of formula (12) or (13) with a compound of formula $HNR_aR_b$;

wherein $R_2$, $R_a$, $R_b$ and $Lp(D)_n$ are as hereinabove defined and

formulae (10), (11), (12) and (13) are as hereinabove defined.

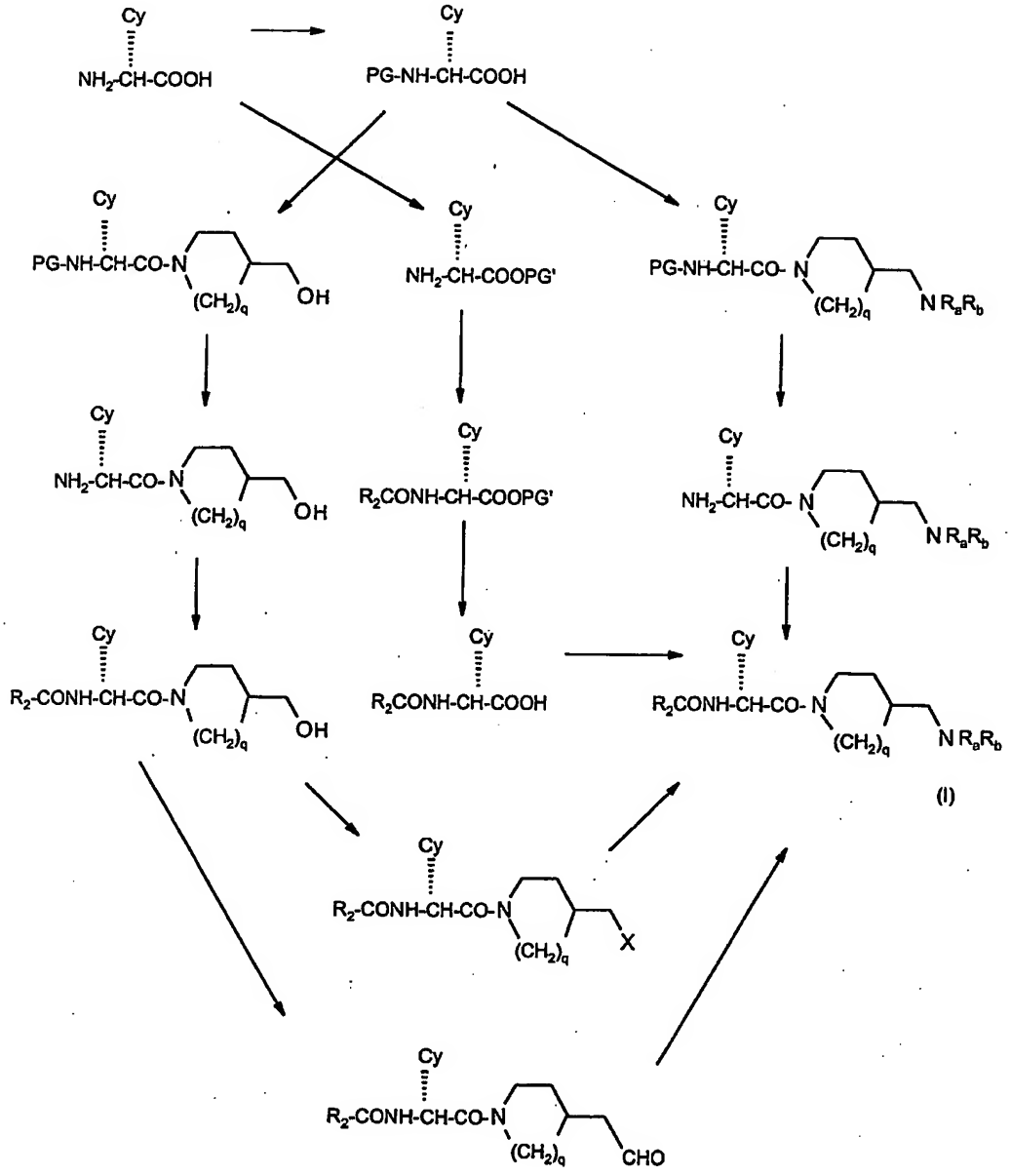
A compound of the formula (12) or (13) may be formed from the corresponding hydroxymethyl compound. Oxidation of the hydroxymethyl compound with a suitable mild oxidising agent for the formation of aldehydes, such as N-methylmorpholine oxide in the presence of tetrapropylammonium perruthonate, can be used to form a compound of the formula (12).

Other possible oxidising agents include manganese dioxide or DMSO/oxalyl chloride or DMSO/$SO_3$ or Dess-Martin reagent.

A compound of formula (13) can be formed from the hydroxymethyl compound by introducing the leaving group X. When X is mesyloxy or tosyloxy, the hydroxymethyl compound may be reacted with the mesyl or tosyl halide in the presence of an organic base, such as triethylamine, in an inert organic solvent such as dichloromethane.

When -X-X is -CONH- and Y is CH, a compound of formula (I) may be prepared by a number of steps from an amino acid derivative using the reactions described above. For example, see Scheme I

Scheme 1




PG is an amino-protecting group
PG' is a carboxy-protecting group

An amino acid from Scheme I may be prepared (for example) by one or more of the following methods:

(i) from aryl or heteroaryl aldehydes via the Strecker synthesis or modifications thereof, via Bucherer-Bergs hydantoin synthesis, or via the Ugi methodology ("Isonitrile Chemistry", Ugi I. Ed.; Academic: New York, 1971;145-1999, ``Multicomponent Reactions with Isocyanides'', Domling, A.;

Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168; ``Amino Acid Derivatives by Multicomponent Reactions'', Dyker, G. *Angew, Chem. Int. Ed. Engl.* **1997**, 36, 1700; and also see ``A new Class of Convertible Isocyanides in the Ugi Four-Component Reaction'', Lindhorst, T.; Bock H.; Ugi, I. *Tetrahedron*, **1999**, 55, 7411.) with removal and replacement of protecting groups;

(ii) from styrenes via Sharpless methodology (J. Am. Chem. Soc. 1998,120, 1207-1217)

(iii) from aryl boronic acids via Petasis methodology (Tetrahedron, 1997, 53, 16463-16470) with removal and replacement of protecting groups;

(iv) from aryl and heteroaryl acetic acids - via Evan's azidation (Synthesis, 1997, 536-540) or by oximation, followed by reduction and addition of protecting groups; or

(v) from existing aryl glycines by manipulation of functional groups, for example, alkylation of hydroxy groups, palladium assisted carbonylation of triflates derived from hydroxy groups and further manipulation of the carboxylic esters to give carboxylic acids by hydrolysis, carboxamides by activation of the carboxylic acid and coupling with amines, amines via Curtius reaction on the carboxylic acid or

(vi) from aliphatic, carbocylic and non-aromatic heterocyclic aldehydes and ketones using a Horner-Emmons reaction with N-benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (Synthesis, 1992, 487-490), or by any other method known in the art.

A starting material for the preparation of a compound of formula (I), where the alpha atom is nitrogen, may be produced, for example, by reaction of a beta protected hydrazine (such protection to be chosen as to be compatible with the subsequent reagents to be employed) with phosgene, diphosgene, triphosgene or N,N'carbonyl diimidazole to give a reactive compound of the type PGNHN(Cy)COCl or PGNHN(Cy)CO-imidazole (wherein PG is a protecting group).

This intermediate may be used as has been described above

for the carboxylic starting reagents where the alpha atom is carbon.

The skilled person will be aware that at certain stages in the synthesis of a compound of formula (I) it may be necessary to protect a reactive functional group in the molecule to prevent unwanted side-reactions.

The protection of amino and carboxylic acid groups is described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxy protecting groups include $C_1$-$C_6$ alkyl groups such as methyl, ethyl, t-butyl and t-amyl; aryl($C_1$-$C_4$)alkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and t-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine protecting groups (PG) include acyl groups, such as groups of formula RCO in which R represents $C_{1-6}$ alkyl, $C_{3-10}$ cycloalkyl, phenyl $C_{1-6}$ alkyl, phenyl, $C_{1-6}$ alkoxy, phenyl $C_{1-6}$ alkoxy, or a $C_{3-10}$ cycloalkoxy, wherein a phenyl group may be optionally substituted, for example by one or two of halogen, $C_1$-$C_4$ alkyl and $C_1$-$C_4$ alkoxy.

Preferred amino protecting groups include benzyloxycarbonyl (CBz), t-butoxycarbonyl (Boc) and benzyl.

In another aspect the invention relates to a process for preparing a compound of formula I comprising deprotecting a compound of formula (I'):

$$R^{2'}\text{-}X\text{-}X\text{-}Y(Cy')\text{-}L\text{-}Lp(D)_n' \qquad (I)'$$

Wherein $R^{2'}$ is $R^2$ (as hereinabove defined) or protected $R^2$, Cy' is Cy (as hereinabove defined) or protected Cy and $Lp(D)_n'$ is $Lp(D)_n$ (as hereinabove defined) or protected $Lp(D)_n$; providing at least one protecting group is present.

If necessary physiologically tolerable salts can be formed using methods known in the art.

All novel intermediates described herein are provided as further aspects of the invention.

The compounds of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature or transdermally. The compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. Preferably the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

The following are examples of pharmaceutical compositions of compounds according to the invention.

**Formulation 1**

Hard gelatin capsules are prepared using the following ingredients:

| | Quantity (mg/capsule) |
|---|---|
| Active Ingredient | 250 |
| Starch, dried | 200 |
| Magnesium stearate | 10 |
| Total | 460 mg |

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

**Formulation 2**

Tablets each containing 60 mg of active ingredient are made as follows:

| | |
|---|---|
| Active Ingredient | 60 mg |
| Starch | 45 mg |
| Microcrystalline cellulose | 35 mg |
| Polyvinylpyrrolidone | 4 mg |
| Sodium carboxymethyl starch | 4.5 mg |
| Magnesium stearate | 0.5 mg |
| Talc | 1 mg |
| Total | 150 mg |

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Viewed from this aspect the invention provides a pharmaceutical composition comprising a serine protease inhibitor according to the invention together with at least one pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may also optionally comprise at least one further antithrombotic and/or thrombolytic agent.

Viewed from a further aspect the invention provides the use of a serine protease inhibitor according to the invention for the manufacture of a medicament for use in a method of

treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat (i.e. treat or prevent) a condition responsive to said inhibitor.

Viewed from a further aspect the invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a serine protease inhibitor (e.g. a condition such as a thrombotic disorder responsive to a factor Xa inhibitor), said method comprising administering to said body an effective amount of a serine protease inhibitor according to the invention.

The dosage of the inhibitor compound of the invention will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However in general, quantities of from 0.01 to 100 μmol/kg bodyweight will be administered.

All publications referred to herein are hereby incorporated by reference.

The invention will now be described further with reference to the following non-limiting Examples.

**Experimental**

Abbreviations used follow IUPAC-IUB nomenclature. Additional abbreviations are HPLC, high-performance liquid chromatography; rpHPLC, reverse phase HPLC; SCX, strong cation exchange resin; THF, tetrahydrofuran; HOAc, acetic acid; DMSO, dimethyl sulfoxide (perdeuterated if for NMR); EtOAc, ethyl acetate; EtOH, ethanol; DMF, dimethylformamide; DCM, dichloromethane; HAOT, 1-hydroxy-7-azabenzotriazole; HOBT, 1-hydroxy benzotriazole, EDCI, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DIPEA, diisopropylethylamine; Boc, tertiary butyloxycarbonyl; TEA, triethylamine; TFA, trifluoroacetic acid; MALDI-TOF, Matrix assisted laser desorption ionisation-time of flight mass spectrometry, CI-MS, chemical ionization mass spectrum; API-MS (atmospheric pressure chemical ionization mass spectra) were obtained on a PEsciex (trademark) API 150EX with a heated nebulizer and nitrogen as the reagent gas in positive ion mode. RT, retention time; TLC, thin layer chromatography with $R_f$ as relative mobility. All solution concentrations are expressed as %Vol./%Vol. unless otherwise stated. Reagents were obtained from a variety of commercial sources.

IR means an infrared spectrum was obtained. $^1$NMR, 1H-NMR, or 1H NMR means a proton magnetic resonance spectrum was obtained.

In general in this specification, "D-" or "R-" in the name of a product indicates the product was made beginning with a chiral starting material, for example D-phenylglycine; however, racemization may have occurred, and the enantiomeric purity may not have been determined.

**General Experimental Procedures:**

**Purification of Compounds (rpHPLC chromatography)**
Material was purified using standard reverse-phase preparative chromatography techniques. A 5 micron, 20 x 50 mm O.D. C18 column was used (YMC ODS-A) with a flow rate of 20 mL/min and

an standard elution time of 10-15 minutes. A gradient of water:acetonitrile (between 95:5 to 5:95; each eluent w/0.1% TFA) over the elution time was used. Fractions containing product were concentrated, frozen, and lyophilized to afford, when applicable, the trifluoroacetate salt of the product. The free base could be obtained, if desired, by loading a methanolic solution of the trifluoroacetate salt onto an ion-exchange resin (SCX, Varian) and subsequent elution of the resin with methanol followed by 2N ammonia in methanol. Concentration of the later fractions afforded the free base product. Preparation of a hydrochloride salt from the free base was completed by treatment an organic solution of the free base (EtOAC, methylene chloride) with anhydrous HCl in diethyl ether and concentration.

**Preparation of Starting Materials and Intermediates**

Intermediate substituted glycine compounds for starting materials and intermediates, including those in which the amino group and/or the carboxy group is protected, conveniently may be prepared using one of the procedures below, or by a similar procedure. It may be convenient or preferred to change the order of steps in the preparation of a compound of the invention and to use a similar procedure with a different intermediate. In particular, it may be convenient to use an acyl group $R_2$-CO- initially in a preparation, rather than an amino protecting group.

Abbreviations, in addition to others listed herein, include: TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical; (DHQD)2PHAL: hydroquinidine 1,4-phthalazinediyl diether; r.b., round bottomed;

**Preparation of Intermediates KE-1 - KE-3**

The following compounds were prepared according to the indicated method (Method KE-A) from the indicated starting materials, unless otherwise described.

**Intermediate KE-1**

**Ethyl oxo-quinolin-8-yl-acetate.**

**Method KE-A**

To a stirring solution of 8-bromoquinoline (10.1 g, 48.5 mmol) in THF (500 mL) at -78 °C was added dropwise a 1.3 M solution of sec-butyl lithium (37.3 mL, 48.5 mmol) in cyclohexane. After 5 min, diethyl oxalate (8 mL, 58.3 mmol) was added; and the solution was allowed to slowly warm to room temperature overnight. The next morning, the reaction was quenched with the addition of saturated aqueous $NH_4Cl$; and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and satd aq. $NaHCO_3$; the layers were separated; and then the aqueous phase was washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed over silica gel, eluting with 20% ethyl acetate/hexanes through 25% ethyl acetate/hexanes. The product containing fractions were combined and concentrated in vacuo to give 5.88 g (53%) of the title compound.

1H-NMR
IS-MS, m/e 230.1 (M+1)

**Intermediate KE-2**

**Ethyl oxo-quinolin-5-yl-acetate.**

Prepared from 5-bromoquinoline and diethyl oxalate using Method KE-A.

1H-NMR
IS-MS, m/e 230.0 (M+1)

**Intermediate KE-3**

**Ethyl oxo-thiazol-5-ylacetate.**

To a r.b. flask (500 $cm^3$) under argon, fitted with ethanol thermometer, septum cap, and dropping funnel, was added anhydrous ether (100 $cm^3$) with stirring. This was cooled to -78C and 2M n-butyllithium (60 $cm^3$, 120 mmol) was added.

A solution of silyl thiazole (16g, 16$cm^3$, 100 mmol) in

anhydrous ether (100 $cm^3$) was then added by dropping funnel over 30 minutes. This was allowed to stir for 1 hour to give a peach suspension. To this, was added diethyl oxalate (16.3 $cm^3$, 17.5g, 120 mmol) rapidly to give a brown solution, resulting in a temperature increase to -30 °C. This was allowed to cool back to -78 °C and stirred for 30 minutes. Reaction monitored by $^1H$ NMR ($CDCl_3$).

The brown solution was poured onto 5% hydrochloric acid solution (300 $cm^3$) with vigorous stirring for 30 minutes. Ether layer was separated and washed with saturated bicarbonate (*ca.* 80 $cm^3$), dried over magnesium sulphate, and concentrated *in vacuo* to give an orange oil. This was purified by flash chromatography (10% ethyl acetate/hexane) to give a yellow oil (7.31g, 39.47 mmol) [40% Yield].

$^1H$ NMR ($CDCl_3$); 1.42 (3H, t), 4.45 (2H, q), 8.89 (1H, s), 9.10 (1H, s).

**Preparation of Intermediates OX-1 - OX-7**

The following compounds were prepared according to the indicated method (Method OX-A or Method OX-B) from the indicated starting materials unless otherwise described.

**Intermediate OX-1**

**Ethyl Hydroxyimino-pyridin-2-yl-acetate.**

**Method OX-A**

To a stirring solution of ethyl 2-pyridylacetate (12.6 g, 76.3 mmol) in acetic acid (19 mL) at 5 °C was added a solution of sodium nitrite (6.05 g, 87.7 mmol) in water (12 mL) at a rate sufficient to maintain the internal temperature below 15 °C. After complete addition and an additional 30 min, an additional 30 mL of water were added. The resulting white precipitate was filtered, washed with water, satd aq. $NaHCO_3$, and again with water. The solid was then dried under vacuum to give 14.1 g (95%) of the title compound.

1H-NMR

IS-MS, m/e 194.9 (M+1)

Analysis for $C_9H_{10}N_2O_3$:

Calcd: C, 55.67; H, 5.19; N, 14.43;

Found: C, 55.79; H, 5.14; N, 14.13.

**Intermediate OX-2**

**Ethyl Hydroxyimino-pyridin-3-yl-acetate.**

Using the procedure of Tikk et al [Acta. Chimica, Hungarica, 114(3-4), 355], a mixture of ethyl hydroxyimino-pyridin-3-yl-acetate and n-butyl hydroxyimino-pyridin-3-yl-acetate was prepared from ethyl 3-pyridinyl-acetate and n-butyl nitrite.

1H-NMR

IS-MS, m/e 195 (M+1), 223.1 (M+1)

**Intermediate OX-3**

**Ethyl Hydroxyimino-quinolin-8-yl-acetate.**

**Method OX-B**

To a stirring solution of ethyl oxo-quinolin-8-yl-acetate (5.5 g, 24 mmol) in ethanol (140 mL) was added sodium acetate (2.16 g, 26.4 mmol) followed by hydroxylamine hydrochloride (2.67 g, 38.4 mmol). The mixture was heated to reflux; and, after 7 h, the heating mantle was removed and the solution was allowed to stir overnight at room temperature. The next morning, the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and satd aq. $NaHCO_3$. The layers were separated and the organic phase was washed with brine, dried with $Na_2SO_4$, filtered and concentrated in vacuo. The resulting foam was recrystalized from dichloromethane/hexanes to give an initial crop of 2.5 g of the title compound as an off-white solid, followed by 0.31 g of a second crop. The mother liquor was then concentrated in vacuo, the residue was dissolved in a minimal amount of dichloromethane. The solution was then chromatographed over silica gel, eluting with 30% ethyl acetate/hexanes, then 40% ethyl acetate/hexanes, and finally with ethyl acetate. The product containing fractions were combined and concentrated in

vacuo to give 1.94 g of the title compound for a combined yield of 4.75 g (81%).

1H-NMR
IS-MS, m/e 245.0 (M+1)

**Intermediate OX-4**

**Ethyl Hydroxyimino-quinolin-5-yl-acetate.**

**Prepared from ethyl oxo-quinolin-5-yl-acetate using Method OX-B.**

1H-NMR
IS-MS, m/e 245.0 (M+1)

**Intermediate OX-5**

**Ethyl Hydroxyimino-thiazol-5-ylacetate.**

To a r.b. flask (500 $cm^3$) was added the ethyl oxo-thiazol-5-ylacetate (6.30g, 34.02 mmol) to ethanol (*ca.* 180 $cm^3$) with stirring. Sodium acetate (3.06g, 37.30 mmol) and hydroxylamine hydrochloride (3.78g, 54.43 mmol) were then added to give an off-white suspension. This was brought to reflux at 85C for 1 hour. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.5, prod. r.f. 0.3.). Reaction cooled and concentrated *in vacuo*. Product taken up in ethyl acetate (*c.a.* 200 $cm^3$) and washed with 5% hydrochloric acid solution. Ethyl acetate layer was dried over magnesium sulphate and evaporated to dryness to give a cream solid (6.372g, 31.825 mmol) [94% Yield].

$^1H$ NMR ($CDCl_3$); 1.40 (3H, m), 4.40 (2H, m), 8.06 ($^1/_3H$, s), 8.78 ($^1/_3H$, s), 8.95 ($^2/_3H$, s), 8.98 ($^2/_3H$,s).

**Intermediate OX-6**

**Ethyl α-Oximino-thiazole-4-acetate.**

To a 2 necked r.b. flask (100 $cm^3$) with ethanol thermometer, concentrated sulphuric acid (25 $cm^3$) was added

and cooled to 0 °C with stirring. To this solution was added the ethyl-α-oximino-2-aminothiazole-4-acetate (5.00g, 23.231 mmol). Water (10 $cm^3$) was then added and cooled to -10 °C. A solution of sodium nitrite (1.683g, 24.393 mmol) in water (5 $cm^3$) was then added slowly over an hour keeping the temperature below -5°C.

To a separate r.b. flask (500 $cm^3$), water (180 $cm^3$) was added and cooled to 3°C. The reaction solution was poured in to the cold water with stirring and then cooled to -5°C. To this solution, 50% hypophosphoric acid (90 $cm^3$) was added dropwise over 10 minutes keeping the temperature at -5 °C. The solution was allowed to warm to room temperature and stirred overnight. The product was extracted with diethyl ether (*ca.* 3x150 $cm^3$) and washed with water. The ether layer was concentrated *in vacuo* and treated to flash chromatography (50% ethyl acetate/n-hexane) to yield a orange oil upon concentration *in vacuo* (0.60g, 3.00 mmol) [13% yield].

$^1H$ NMR ($CDCl_3$) 1.35 (3H, m), 4.35 (2H, m), 8.4 (1H, s), 8.9 (1H, s), 14.4 (1H, s).

**Intermediate OX-7**

**Ethyl α-Oximino-2-methylthiazole-4-acetate.**

This was prepared from ethyl-γ-chloro-α-oximino-acetoacetate (1.44g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry*, **1973**, 16(9), 978-984) to yield the titled compound (0.64g).

$^1H$ NMR ($CDCl_3$) 1.35 (3H, t), 2.7 (3H, s), 4.35 (2H, q), 8.2 (1H, s).

**Ethyl γ-Chloro-α-oximinoacetoacetate.**

This was prepared from ethyl oximinoacetoacetate (1.73g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry*, **1973**, 16(9), 978-984) to yield the titled compound

(1.44g).

$^1$H NMR ($CDCl_3$) 1.25 (3H, t), 4.3 (2H, q), 4.55 (2H, s), 9.45 (1H, s), contains 20% starting material by NMR.

**Ethyl Oximinoacetoacetate**

This was prepared from ethyl acetoacetate (10.00g) using the method of Fischer (*Organic Synthesis Coll. Vol. 3*, 513-516) to yield the titled compound (12.45g).

$^1$H NMR ($CDCl_3$) 1.25 (3H, t), 2.35 (3H, s), 4.3 (2H, q), 8.8 (1H, br.).

**Preparation of Intermediates AL-1 - AL-3**

The following compounds were prepared according to the indicated method (Method AL-A or Method AL-B) from the indicated starting materials, unless otherwise described.

**Intermediate AL-1**

**R-3-Bromo-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene.**

Method AL-A

Sodium hydroxide (3.33 g, 83.25 mmol) was dissolved in water (220 mL), and 20 mL of the resulting solution was removed and added to potassium osmate (410 mg, 1.11 mmol). The remaining sodium hydroxide solution (200 mL) was added to a stirred solution of *t*-butyl carbamate (9.9 g, 84.5 mmol) in *n*-propanol (110 mL) followed by freshly prepared *t*-butyl hypochlorite (9.65 mL; 83.5 mmol). After stirring for 5 min, the solution was cooled to 0 °C. A solution of $(DHQD)_2PHAL$ (1.30 g, 1.67 mmol) in *n*-propanol (110 mL) was added, followed by a solution of 3-bromostyrene (5 g, 27.31 mmol) in n-propanol (220 mL), followed by dropwise addition of the potassium osmate/sodium hydroxide solution. The reaction was stirred overnight. Saturated aqueous sodium sulfite (150 mL) was added, and the reaction was stirred for 15 min. The aqueous layer was separated and extracted with ethyl acetate

(3x 200 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvent under vacuum gave the crude product which was purified by chromatography (silica, 3:2 hexane:ethyl acetate then rechromatographed loading with toluene, gradient elution with hexane - 4:1 hexane:ethyl acetate) to give the title product (4.18 g, 49%).

Melting Point = 90-91 °C
$^1H$ NMR ($CDCl_3$).

**Intermediate AL-2**

**R-3-Methoxycarbonyl-(1-t-butoxycarbonylamino-2-hydroxy-ethyl)benzene.**

**Method AL-B**

In a glass liner containing a stirrer bar was placed $Pd(OAc)_2$ (871 mg, 3.88 mmol), $PPh_3$ (1.96 g, 7.47 mmol, NaOAc (1.48 g, 18.04 mmol) and DMF (82 mL). To this stirred solution was added a solution of R-3-bromo-(1-t-butoxy-carbonylamino-2-hydroxyethyl)benzene (4.27 g, 13.5 mmol) in MeOH (82 mL). The resulting solution was purged with nitrogen and placed in a stirred pressure vessel. The system was charged to 4.1 bar (60 psig) of CO and heated at 95 °C for 36 h. The mixture was cooled to room temperature, filtered through diatomaceous earth, and partitioned between ethyl acetate and water. The organic layer was washed with water (3x) and brine (1x) and dried over $MgSO_4$. Removal of solvent under vacuum gave the crude product which was purified by chromatography (silica gel, gradient elution with 30-35% ethyl acetate/hexane) to provide the title product (3.53 g, 89%).

Melting Point = 73-75 °C with decomposition
$^1H$ NMR ($CDCl_3$).

API-MS, m/e = 240 ($M-C_4H_9+1$).

**Intermediate AL-3**

**R-3-Cyano-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene.**

**Prepared from 3-cyanostyrene using Method AL-A.**

**3-Cyanostyrene was prepared using the method described below.**

Melting Point = 76 °C.

$^1H$ NMR ($CDCl_3$).

**Preparation of 3-Cyanostyrene**

To a stirred suspension of methyltriphenylphosphonium bromide (75 g, 209.71 mmol) in dry THF (750 mL) at 0 °C under nitrogen was added dropwise *n*-BuLi (83 mL, 2.5 M in hexanes, 207.50 mmol). The mixture was warmed to room temperature. 3-Cyanobenzaldehyde (25 g, 190.65 mmol) was added as a solid in 5 g batches, and the mixture was stirred at room temperature overnight. The reaction was quenched in water, and the solvent was removed under vacuum. The residue was dissolved in the minimal amount of THF, and triphenylphosphine oxide was precipitated using ether. The solid was filtered through diatomaceous earth, and the filtrate was concentrated. Distillation by Kugelrhor at 90 °C/33 Pa (0.25 mm Hg) gave the product as a colorless oil (15.5 g, 62%).

Boiling Point = 90 °C at 0.25 mmHg.

$^1H$ NMR ($CDCl_3$).

**Preparation of Intermediates PAE-1 - PAE-16**

The following compounds were prepared according to the indicated method (Method PAE-A, Method PAE-B, Method PAE-C, Method PAE-D or PAE-E) from the indicated starting materials,

unless otherwise described.

**Intermediate PAE-1**

**Boc-D,L-(2-pyridinyl)glycine Ethyl Ester.**

**Method PAE-A**

To a solution of ethyl hydroxyimino-pyridin-2-yl-acetate (7.8 g, 40.15 g) in ethanol (175 mL) and glacial acetic acid (20 mL) was added 5% Pd/C, and the mixture was shaken in a hydrogenation apparatus under an atmosphere of hydrogen at 4.1 bar (45 psig) for 4 h. The mixture was filtered through diatomaceous earth and concentrated in vacuo. The residue was dissolved in THF/$H_2O$ (1/1, 240 mL) and treated with di-tert-butyl dicarbonate (14.23 g, 65.2 mmol) and sodium bicarbonate (27.4 g, 326 mmol). After stirring at room temperature for 2 h, the solution was concentrated in vacuo and the residue was partitioned between EtOAc and water. The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified via chromatography over silica gel, eluting with a stepwise gradient of 10-20% ethyl acetate in dichloromethane to give 8.11 g (72%) of the title compound as a yellow oil.

1H-NMR
IS-MS, m/e 281.1 (M+1)

**Intermediate PAE-2**

**Boc-D,L-(3-pyridinyl)glycine Ethyl Ester.**

Prepared from ethyl hydroxyimino-pyridin-3-yl-acetate using Method PAE-A.

1H-NMR
IS-MS, m/e 281.1 (M+1)

**Intermediate PAE-3**

**Boc-D,L-(8-quinolinyl)glycine Ethyl Ester.**

**Method PAE-B**

To a stirring solution of ethyl hydroxyimino-quinolin-8-yl-acetate (2.4 g, 9.8 mmol) in 50% aq. formic acid (50 mL) at 0 °C

was added zinc dust (2 g, 31 mmol). After 1 min, the mixture was filtered through diatomaceous earth and the filtrate was loaded onto an SCX column. After washing the column with methanol, the product was eluted with a 3 to 1 mixture of dichloromethane and (2 N $NH_3$ in methanol). The product containing fractions were combined and concentrated in vacuo to give 2.24 g of light orange oil (IS-MS, m/e 231.0 (M+1)).

The oil (2.14 g, 9.3 mmol) was dissolved in THF (40 mL) and to this stirring solution was added triethylamine (1.4 mL, 10.2 mmol), followed by di-tert-butyl-dicarbonate (2.1 g, 9.8 mmol). After 45 min, the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic phase was then washed with satd aq. $NaHCO_3$, dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was dissolved in a minimum volume of dichloromethane and chromatographed over silica gel, eluting with 5% ethyl acetate in hexanes. The product containing fractions were combined and concentrated to give 2.5 g (81%) of the title compound.

1H-NMR
IS-MS, m/e 331.0 (M+1)

**Intermediate PAE-4**
**Boc-D,L-(5-quinolinyl)glycine Ethyl Ester**

Prepared from ethyl hydroxyimino-quinolin-5-yl-acetate using Method PAE-B.

1H-NMR
IS-MS, m/e 331.0 (M+1)

**Intermediate PAE-5**
**N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(2-trifluoro-methylphenyl)glycine Methyl Ester.**

**Method PAE-C**

To 2-trifluoromethylbenzaldehyde (1 g, 5.7 mmol) with stirring was added 2,4-dimethoxybenzylamine (0.86 mL, 5.7 mmol) and methanol (2 mL). After 5 min, the solution was diluted with toluene 100 mL and concentrated in vacuo (twice). The residue

was then dissolved in anhydrous methanol (12 mL) and 1,1-dimethyl-2-(methoxycarbonyloxy)ethyl isonitrile [Tetrahedron, 55 (1999) 7411-7420] (0.9 g, 5.7 mmol) was added, followed by 4-methoxybenzoic acid (0.87 g, 5.7 mmol). After stirring for 72 h, the solvent was removed in vacuo and the residue was chromatographed over silica gel, eluting with a step gradient of 30% ethyl acetate in hexanes through 50% ethyl acetate in hexanes. The product containing fractions were combined and concentrated in vacuo; and then the residue was dissolved in ethyl acetate, washed with satd aq. $NaHCO_3$, dried with $Na_2SO_4$, filtered and concentrated to give 1.76 g (48%) of thick oil (NMR, IS-MS, m/e 633.0 (M+1)).

The oil (0.5 g, 0.79 mmol) was then dissolved in toluene (5 mL) and concentrated in vacuo (twice) to give a white foam. The residue was then dissolved in THF (3 mL) and potassium tert-butoxide (0.11 g, 0.95 mmol) was added. After 15 min, 12 N HCl (0.079 mL, 0.95 mmol) was added and the solution was allowed to stand overnight in the refrigerator. The next morning, the solvent was removed and the residue was chromatographed over silica gel, eluting with 30% ethyl acetate in hexanes. The product containing fractions were combined and concentrated to give 0.32 g (79%) of the title compound.

1H-NMR

IS-MS, m/e 518.0 (M+1)

**Intermediate PAE-6**

**BOC-D,L-(5-thiazolyl)glycine ethyl ester.**

To a r.b. flask (250$cm^3$), D,L-(5-thiazolyl)glycine ethyl ester (4.60g, 24.7 mmol) was added to tetrahydrofuran (*c.a.* 100$cm^3$) with stirring to give a yellow solution. BOC anhydride (5.439g, 24.948 mmol) and triethyl amine (3.79 $cm^3$, 2.75g, 27.17 mmol) were then added with stirring for 1 hour. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.05, prod. r.f. 0.5.). The reaction concentrated *in vacuo* and product taken up in ethyl acetate (*c.a.* 150 $cm^3$), washed with 5% hydrochloric acid solution (*c.a.* 30 $cm^3$), and saturated

bicarbonate (*ca.* 30cm$^3$). Ethyl acetate layer was dried over magnesium sulphate and evaporated to dryness to give an orange oil (7.42g, ~24.70 mmol) [~100% Yield].

$^1$H NMR ($CDCl_3$); 1.30 (3H, t), 1.48 (9H, s), 4.28 (2H, q), 5.68 (1H, br.), 7.88 (1H, s), 8.78 (1H, s).

**D,L-(5-Thiazolyl)glycine Ethyl Ester.**

To a r.b. flask (250 cm$^3$), was added 5-thiazolyl-oximinoacetic acid ethyl ester (6.37g, 31.825 mmol) to ethanol (*c.a.* 80cm$^3$) with stirring. 50% Formic acid solution (50 cm$^3$) was added with zinc dust (5.10g, 81.83 mmol) and allowed to stir overnight. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.3, prod. r.f. 0.05.). Reaction solution filtered over celite and filtrate concentrated *in vacuo*. This was basified to pH 9 with anhydrous potassium carbonate and product taken up in 3:1 chloroform/isopropanol solution (*c.a.* 200 cm$^3$). This was washed with saturated bicarbonate (*c.a.* 50 cm$^3$), dried over magnesium sulphate and concentrated *in vacuo* to give a brown oil (4.60g, 24.70 mmol) [78% Yield].

$^1$H NMR ($CDCl_3$); 1.25 (3H, t), 1.95 (2H, br.), 4.22 (2H, q), 4.85 (1H, s), 7.80 (1H, s), 8.70 (1H, s).

**Intermediate PAE-7**

**N-Boc-D,L-(4-thiazolyl)glycine ethyl ester**

To a solution of D,L-(4-thiazolyl)glycine ethyl ester (0.460g, 2.470 mmol) in tetrahydrofuran (20 cm$^3$), was added di-*tert*-butyl dicarbonate (0.530g, 2.470 mmol) and triethylamine (0.344 cm$^3$, 2.470 mmol). This was allowed to stir for 1 hour and the solution concentrated *in vacuo*. The oil was taken up in ethyl acetate (*c.a.* 50 cm$^3$) washed with 0.5% hydrochloric acid solution (*c.a.* 20 cm$^3$), and saturated sodium bicarbonate solution (*c.a.* 20 cm$^3$). This was then dried over magnesium sulphate and concentrated *in vacuo* to yield an orange oil

(0.709g, 2.477 mmol) [~100% yield].

$^1H$ NMR ($CDCl_3$) 1.15 (3H, t), 1.35 (9H, s), 4.1 (2H, m), 5.45 (1H, d), 5.75 (1H, d), 7.3 (1H, d), 8.7 (1H, d).

**D,L-(4-Thiazolyl)glycine Ethyl Ester.**

This was prepared from ethyl-α-oximino-thiazole-4-acetate (0.60g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry,* 1973, 16(9), 978-984) to yield the titled compound (0.46g).

$^1H$ NMR ($CDCl_3$) 1.25 (3H, t), 1.8-2.3 (2H, br.), 4.1 (2H, m), 4.75 (1H, s), 7.25 (1H, d), 8.7 (1H, d).

**Intermediate PAE-8**

**N-Boc-D,L-(2-methylthiazol-4-yl)glycine Ethyl Ester**

To a solution of D,L-(2-methylthiazol-4-yl)glycine ethyl ester (0.397g, 1.982 mmol) in tetrahydrofuran (20 $cm^3$), was added di-*tert*-butyldicarbonate (0.475g, 2.180 mmol) and triethylamine (0.304 $cm^3$, 2.180 mmol). This was allowed to stir for 1 hour and the solution concentrated *in vacuo*. The oil was taken up in ethyl acetate (*c.a.* 50 $cm^3$) washed with 0.5% hydrochloric acid solution (*c.a.* 20 $cm^3$), and saturated sodium bicarbonate solution (*c.a.* 20 $cm^3$). This was then dried over magnesium sulphate and concentrated *in vacuo* to yield a yellow oil (0.654g, 2.177 mmol) [~100% yield].

$^1H$ NMR ($CDCl_3$) 1.1 (3H, s), 1.35 (9H, s), 2.6 (3H, s), 4.15 (3H, m), 5.3 (1H, d), 5.7 (1H, s), 7.0 (1H, s).

**D,L-(2-Methylthiazol-4-yl)glycine Ethyl Ester.**

This was prepared from ethyl-α-oximino-2-methylthiazole-4-acetate (0.62g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry,* **1973**, 16(9), 978-984) to yield the titled compound (0.40g).

$^1H$ NMR ($CDCl_3$) 1.15 (3H, t), 1.95 (2H, br.), 2.6 (3H, s), 4.15 (2H, m), 4.65 (1H, s), 6.95 (1H, s).

**Intermediate PAE-9**

**Boc-R-(4-Hydroxyphenyl)glycine methyl ester**

To a stirred mixture of R-(4-hydroxyphenyl)glycine methyl ester hydrochloride (14g) and sodium bicarbonate (11.7g) in THF (150ml) and water (50ml), was added in one portion, di- t-butyl dicarbonate (15.9g). The mixture was stirred rapidly to allow thorough mixing for 4h. Hexane (75ml) was added and the organic layer separated and washed with sat. sodium bicarbonate solution, then brine and then dried with magnesium sulphate. The drying agents was filtered off and washed with a little THF and evaporated to dryness, finishing with a high vacuum pump to remove the last traces of di- t-butyl dicarbonate. Yield 19.7g, 96%.

$^1H$ NMR

**R-(4-Hydroxyphenyl)glycine Methyl Ester Hydrochloride.**

To a dry 250ml three necked round bottom flask, equipped with a low temperature thermometer, a septum for nitrogen coverage and another for introduction of thionyl chloride by syringe, was added R-4-hydroxyphenylglycine (12.5g) and dry methanol (24ml). The mixture was stirred (magnetic stirrer) and cooled to an internal temperature of -20°C using cardice/acetone. Using a syringe, thionyl chloride was added dropwise to the cooled mixture over a period of 10min. (Care: the reaction of thionyl chloride with methanol is very exothermic and rate of addition should be such that the thionyl chloride is efficiently stirred into the mixture and that the temperature does not rise above -20°C. Once the addition was complete the mixture was allowed to warm to room temperature overnight (16-18hr). Dry ether (150ml) was added and the white ppt. that formed was filtered off, washed with a little more ether and dried. Yield 15.5g 95%.

$^1H$ NMR

**Intermediate PAE-10**

**Boc-R-(4-Trifluoromethanesulphonyloxyphenyl)glycine Methyl Ester Hydrochloride**

To a stirred solution of Boc-R-(4-hydroxyphenyl)glycine methyl ester 19g in dichloromethane 400ml was added 2,6-lutidine 9.44ml and 4-dimethylaminopyridine 1.65g and the mixture cooled in an ice bath. Trifluoromethananesulphonic anhydride 13.74ml was added over a period of 5min and then the reaction left to warm to room temperature over 4h. The organic solution was washed with water, 2 x 150ml, 1N HCl 2 x 150ml and the saturated sodium bicarbonate 150ml. The organics were dried with magnesium sulphate and then evaporated to and oil. The mixture was purified using flash chromatography ($SiO_2$ 250g eluting with 1:1 hexane/dichloromethane and then neat dichloromethane). Pure product fractions were combined and evaporated, finishing with a high vacuum pump to remove all traces of solvent, to give a white solid, 19g 77%.

$^1H$ NMR

**Intermeidate PAE-11**

**Boc-R-(4-Methoxycarbonylphenyl)glycine Methyl Ester.**

**Method PAE-D**

Boc-R-4-trifluoromethanesulphonyloxyphenylglycine methyl ester (15g), methanol (32.6ml), bis-1,3-diphenyl-phosphinylpropane (448mg), palladium (II) acetate (255mg), triethylamine (10.2ml) and dimethylformamide (72ml) were placed in the glass liner of the Parr reactor and the reactor assembled. The vessel was pressurised to ~10psi with nitrogen and the gas released (repeated five times to remove all oxygen from the system). Carbon monoxide gas was then carefully introduced (use extreme care -the gas cylinder is pressurised to far beyond the bursting disc pressure of the Parr, ideally use a pressure regulator to reduce the pressure to ~100psi) to ~20psi and released three times (into the back of a fume

hood). Carbon monoxide was then added to ~100psi and the stirrer started. The vessel was slowly heated to 65°C internal temperature and then stirred at 65°C overnight. (At the early stages more carbon monoxide was added to maintain ~100psi) A sample was removed after 18h and examined by tlc. When complete, the reaction was cooled to ~30°C, the gas released and the vessel flushed five times with nitrogen as before. The reaction mixture was partitioned between ethyl acetate and water and the organic layer washed with 1M hydrochloric acid and then saturated sodium bicarbonate. The solution was dried with $MgSO_4$ and evaporated. Flash chromatography of the resulting oil gave the product, pure by tlc, 10.6g 90%.

$^1H$ NMR

**Intermediate PAE-12**

**Boc-R-(4-Benzyloxycarbonylphenyl)glycine Methyl Ester**

Prepared from Boc-R-4-trifluoromethanesulphonyloxy phenylglycine methyl ester and benzyl alcohol using Method PAE-D.

$^1H$ NMR

**Intermediate PAE-13**

**Boc-R-(4-Carboxyphenyl)glycine Methyl Ester.**

Boc-R-(4-benzyloxycarbonylphenyl)glycine methyl ester (500mg) was dissolved in THF containing Pd/C 10% (100mg) and hydrogenated at 1atm for 2h. Removal of the catalyst by filtration and evaporation of solvent gave Boc-R-(4-carboxyphenyl)glycine methyl ester (330mg, 87%).

$^1H$ NMR

**Intermediat PAE-14**

**Boc-R-(4-carboxamidophenyl)glycine Methyl Ester.**

**Method PAE-E**

To a solution of Boc-R-(4-carboxyphenyl)glycine methyl

ester (3.5g) in DMF 30ml was added EDCI (2.60g 1.36 mmol) and HOBt (1.4g 10.4mmol) and the mixture stirred for 10min before cooling in a ice bath and bubbling in ammonia gas for 5min. The mixture was stirred for 2h at room temperature and then diluted with ethyl acetate and washed with water. The aqueous solution was extracted with a little ethyl acetate and the combined organics washed with brine. The organic solution was evaporated to an oil which was purified by flash chromatography ($SiO_2$ - dichloromethane/ ethyl acetate 0 - 25%) to give Boc-R-(4-carboxamidophenyl)glycine methyl ester (1.7g 48%).

$^1H$ NMR

**Intermediate PAE-15**

**Boc-R-(4-methylcarboxamidophenyl)glycine Methyl Ester.**

Prepared from Boc-R-(4-carboxyphenyl)glycine methyl ester and methylamine using Method PAE-E.

$^1H$ NMR

**Intermediate PAE-16** (pb0-h5u-119, px099940)
**N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(quinolin-4-yl)glycine Methyl Ester.**

Prepared from quinoline-4-carboxaldehyde using Method PAE-C.

$^1H$ NMR

**Preparation of Intermediates PAA-1 - PAA-20**

The following compounds were prepared according to the indicated method (Method PAA-A, Method PAA-B, Method PAA-C, Method PAA-D, or Method PAA-E) from the indicated starting materials, unless otherwise described.

**Intermediat PAA-1**

**Boc-D,L-(2-chlorophenyl)glycine.**

**Method PAA-A**

2-Chlorobenzaldehyde (20 mmol, 2.252 mL) and 2,4-dimethoxybenzylamine (20 mmol, 3.004 mL) were added together and stirred for 2 hours. DCM (5ml) was added and any water separated and removed. tert-Butyl isonitrile (20 mmol, 2.262 mL) was added and stirred for 10mins followed by acetic acid (20 mmol, 1.145 mL). Stirring was continued for 3 days. The reaction mixture was then treated with TFA (30ml) and triethylsilane (5ml). After 3 hours the mixture was evaporated to dryness, 6M HCl (100ml) added and the whole refluxed overnight at 130°C, stirring rapidly. The mixture was allowed to cool and extracted with EtOAc (50ml x2) the aqueous fraction was evaporated to dryness and treated with 2M NaOH solution. The mixture was extracted with EtOAc (50ml x2) excess boc anhydride (5.2g) in dioxane (20ml) was added to the aqueous fraction and stirred overnight. The mixture was extracted with diethyl ether (100ml x2) acidified to pH 1 (cHCl) and extracted with EtOAc (50ml x2). The combined organic fractions were washed with water and evaporated to dryness under high vacuo The product Boc -2-chlorophenyl-glycine (4.252g, 74.5%)

$^1H$ nmr ($CD_3CN/D_2O$) 7.3 (4H, m); 5.5 (1H, s); 1.3 (9H, s). MS 286 (M+1)

**Intermediate PAA-1'**
**(R)-Benzyloxycarbonyl-(2-chlorophenyl)glycine.**

Prepared from 2-chlorostyrene using the method of Sharpless *et al* J.A.C.S. (1998) Vol120 No.6 1207-1217.

**Intermediate PAA-2**

**Boc-D,L-(3-fluorophenyl)glycine.**

Prepared from 3-fluorobenzaldehyde using Method PAA-A.

$^1H$ nmr ($CD_3CN/D_2O$) 7.3 (1H, m), 7.1(3H, m); 5.2 (1H, s); 1.3 (9H, s). MS 270 (M+1)

**Intermediate PAA-3**

**Boc-D,L-(4-fluorophenyl)glycine.**

Prepared from 4-fluorobenzaldehyde using Method PAA-A.

$^1H$ nmr ($CD_3CN/D_2O$) 7.3 (2H, m); 6.9 (2H, m), 5.0 (1H, s); 1.3 (9H, s). MS 270 (M+1)

**Intermediate PAA-4**

**Boc-D,L-(2-methylphenyl)glycine.**

Prepared from 2-methylbenzaldehyde using Method PAA-A.

$^1H$ nmr ($CD_3CN/D_2O$) 7.3 (4H, m); 5.5 (1H, s); 2.5 (3H, s); 1.3 (9H, s). MS 266 (M+1)

**Intermediate PAA-5**

**Boc-D,L-(3-thienyl)glycine.**

Prepared from 3-thiophenecarboxaldehyde using Method PAA-A.

$^1H$ nmr ($CD_3CN/D_2O$) 7.5 (2H, m); 7.1 (1H, d); 5.3 (1H, s); 1.3 (9H, s). MS 258 (M+1)

**Intermediate PAA-6**

**Boc-D,L-(2-fluorophenyl)glycine.**

Was obtained by treating D,L-2-fluorophenylglycine (Aldrich) with Boc anhydride (1.1eq) and 2M NaOH (1eq) in Ethanol. Aqueous work up as described above yielded the protected amino acid.

$^1H$ NMR

**Intermediate PAA-7**

**Boc-D,L-(2-methoxyphenyl)glycine.**

Prepared from 2-methoxybenzaldehyde using Method PAA-A.

$^1H$ NMR

**Intermediate PAA-8**

**Boc-D,L-(2-trifluoromethyl)phenylglycine.**

Prepared from 2-trifluoromethylbenzaldehyde using Method PAA-A.

$^1H$ NMR

**Intermediate PAA-9**

**Boc-D,L-(8-quinolinyl)glycine.**

**Method PAA-B**

To a stirring solution of Boc-D,L-(8-quinolinyl)glycine ethyl ester (2.29 g, 6.93 mmol) in 1,4-dioxane (11 mL) was added a solution of LiOH hydrate (0.32 g, 7.6 mmol) in water. After 2 h, the solvents were removed in vacuo and the residue was dissolved in water and washed with diethyl ether. The aqueous phase was then acidified to pH 3 with solid citric acid and extracted with ethyl acetate. The organic phase was then washed with brine, dried with $Na_2SO_4$, filtered and concentrated to give 2.06 g (98%) of the title compound.

1H-NMR

IS-MS, m/e 303.0 (M+1)

**Intermediate PAA-10**

**Boc-D,L-(5-quinolinyl)glycine.**

Prepared from Boc-D,L-(5-quinolinyl)glycine ethyl ester using Method PAA-B.

1H-NMR

IS-MS, m/e 303.0 (M+1)

**Intermediate PAA-11**

**Boc-D-(3-bromophenyl)glycine.**

Prepared from R-3-bromo-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene using Method PAA-C.

Melting Point = 130-132 °C with decomposition

$^1H$ NMR ($CDCl_3$)

API-MS, m/e = 286 ($M-CO_2H+1$)

**Intermediate PAA-12**

**Boc-D-(3-methoxycarbonylphenyl)glycine.**

**Method PAA-C**

To a stirred solution of R-3-methoxycarbonyl-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene (338 mg, 1.14 mmol) in acetone (7.2 mL) was added 5% $NaHCO_3$ (3 mL). The reaction mixture was cooled to 0 °C. To the stirred suspension was added KBr (14 mg, 0.12 mmol), TEMPO (181 mg, 1.16 mmol) and NaOCl dropwise (2.81 mL, 5.25%). After 1 h at 0 °C, TEMPO (136 mg, 0.88 mmol) and NaOCl (1.09 mL; 5.25%) were added. The reaction was stirred for a further 0.5 h at 0 °C and 5% $NaHCO_3$ (4.3 mL) was added. The reaction was allowed to warm to room temperature overnight. Acetone was removed under vacuum and the crude product was partitioned between ethyl acetate and water. The aqueous layer was washed with ethyl acetate (2x) and acidified to pH 5 with 10% citric acid and extracted with ethyl acetate (4x). The combined organic extracts were dried over $MgSO_4$. Removal of solvent under vacuum gave the product (305 mg, 86%).

$^1H$ NMR ($CDCl_3$)

API-MS, m/e = 254 ($M-C_4H_9+1$)

**Intermediate PAA-13**

**Boc-D-(3-cyanophenyl)glycine.**

Prepared from R-3-cyano-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene using Method PAA-C.

$^1H$ NMR ($CDCl_3$)

API-MS, m/e = 221 ($M-C_4H_9+1$)

**Intermediate PAA-14**

**B c-D-(3-ethanesulfonylaminophenyl)glycine.**

To a stirring solution of 3-—(ethanesulfonylamino-phenyl)glycine (20 g, 77.43 mmol) and sodium carbonate (8.2 g,

77.43 mmol) in 3:1 THF:water (200 mL) at 0 °C, was added di-tert-butyl dicarbonate (18.5 g, 85.17 mmol). After stirring for 30 min, the cold bath was removed; and after an additional 30 min at room temperature the solvent was removed; and the residue was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 2 with $KHSO_4$ and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with $Na_2SO_4$, filtered and concentrated in vacuo to give 17.51 g (63%) of a white solid.

1H-NMR
IS-MS, m/e 357.0 (M-1)

**Intermediate PAA-15**

**N-Boc-D,L-(5-thiazolyl)glycine.**

To a r.b. flask (150 $cm^3$), was added Boc-D,L-(5-thiazolyl)glycine ethyl ester (7.00g, 24.70 mmol) to ethanol (*c.a.* 100$cm^3$) with stirring. 2M Sodium hydroxide solution (25 $cm^3$, 50 mmol) was added and allowed to stir for 1 hour. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.5, prod. r.f. 0.).

Reaction concentrated *in vacuo* and product taken up in saturated bicarbonate (*c.a.* 50 $cm^3$) and washed with ethyl acetate (*c.a.* 30 $cm^3$). Aqueous layer was acidified to pH 2 with concentrated hydrochloric acid and product extracted with 3:1 chloroform/isopropanol solution (*c.a.* 3x60$cm^3$). The organic layer was dried over magnesium sulphate and evaporated to dryness to give an orange solid (4.47g, 17.30 mmol) [74% Yield].

$^1H$ NMR ($CDCl_3$); 1.35 (9H, s), 5.60 (1H, d), 5.83 (1H, d), 7.88 (1H, s), 8.80 (1H, s).

**Intermediate PAA-16**

**N-Boc-D,L-(4-thiazolyl)glycine.**

**Method PAA-D**

To a solution of N-Boc-D,L-(4-thiazolyl)glycine ethyl ester (0.700g, 2.470 mmol) in methanol (*c.a.* 15 $cm^3$), was added 2M sodium hydroxide (2.47 $cm^3$, 4.940 mmol) and allowed to stir for 90 minutes. The solution was concentrated *in vacuo* and taken up in water (*c.a.* 20 $cm^3$). The aqueous solution was washed with ethyl acetate (*c.a.* 20 $cm^3$), and then acidified to pH 2 with 5% hydrochloric acid solution (*c.a.* 50 $cm^3$). The product was extracted with ethyl acetate (*c.a.* 3x30 $cm^3$), dried over magnesium sulphate, and concentrated *in vacuo* to yield a pale yellow oil (0.582g, 2.254 mmol) [91% yield].

$^1H$ NMR ($CDCl_3$) 1.35 (9H, s), 5.5 (1H, d), 5.8 (1H, d), 7.35 (1H, d), 8.75 (1H, d), 9.8-10.2 (1H, br.).

**Intermediate PAA-17**

**N-Boc-D,L-(2-methylthiazol-4-yl)glycine.**

Prepared from N-Boc-D,L-(2-methylthiazol-4-yl)glycine ethyl ester using Method PAA-D.

$^1H$ NMR ($CDCl_3$) 1.35 (9H, s), 2.6 (3H, s), 5.4 (1H, d), 5.9 (1H, s), 7.1 (1H, s).

**Intermediate PAA-18**

**N-Boc-D,L-(2-Benzyloxycarbonylamino-4-thiazolyl)glycine.**

Is prepared from D,L-(2-benzyloxycarbonylamino-4-thiazolyl)glycine. The benzyloxycarbonyl protecting group is removed from the thiazolyl amino group at a convenient point in the preparation of a final compound using a conventional method, such as, for example, heating a solution of an intermediate in HBr/acetic acid at 60 °C, followed by evaporation and a conventional isolation, such as by using SCX ion exchange chromatography.

**D,L-(2-Benzyloxycarbonylamino-4-thiazolyl)glycine** was prepared by the method of Hardy, K.; Harrington, F. and Stachulski, A.

- J. Chem. Soc. Perkin Trans I (1984) 1227-1235.

**Intermediate PAA-19**

**Boc-R-(4-methoxycarbonylphenyl)glycine.**

To a solution of Boc-R-(4-methoxycarbonylphenyl)glycine methyl ester 692mg in THF 10ml was added a solution of lithium hydroxide hydrate 90mg in water 7ml. The mixture immediately became cloudy and over 15min cleared. After 30min, tlc showed the reaction to be complete. Ethyl acetate 20ml and water 20ml were added and the aqueous layer separated. The aqueous solution was acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 x 20ml). The organic solution was then washed with water x 2 and brine x 2, dried with $MgSO_4$ and evaporated to give the mono-ester (650mg, 98%), pure by tlc.

$^1H$ NMR

**Intermediate PAA-20**

**Boc-R-(4-Methoxyphenyl)glycine.**

Boc-R-(4-hydroxyphenyl)glycine methyl ester was converted to Boc-R-4-methoxyphenylglycine using the alkylation method described by Basak *et al.*(Tetrahedron Lett. 1998, 39 (27), 4883-4886) followed by hydrolysis of the methyl ester with lithium hydroxide in aqueous THF.

$^1H$ NMR

**Intermediate PAA-21**

**N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(2-trifluoromethylphenyl)glycine.**

Prepared from N-4-methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(2-trifluoromethylphenyl)glycine methyl ester using Method PAA-B (3 equivalents of LiOH hydrate).

$^1H$ NMR

IS-MS, m/e 503.9 (m + 1)

**Intermediate PAA-22**

**N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)-glycine.**

**Method PAA-E**

To a solution of 2-thiopheneboronic acid (5.0 g, 39.0 mmol, 1 equiv) in 275 mL of methylene chloride at rt was added 3,4-dimethoxybenzylamine (5.89 mL, 39.0 mmol, 1 equiv) followed by glyoxylic acid monohydrate 3.6 g, 39 mmol, 1 equiv). The reaction was allowed to stir for 56 hours at rt after which time the resultant precipitate was filtered and washed with methylene chloride to afford 9.3 g (78%) of N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)glycine as an off-white solid (IS-MS, m/e 308 (m + 1)).

A portion of the solid (5.0 g, 16.3 mmol, 1 equiv.) was dissolved in acetone (20 mL) and 1N sodium hydroxide (20 mL) at rt. To this solution was simultaneously added anisoyl chloride (2.78 g, 16.3 mmol, 1 equiv.) in 20mL of acetone and 2N sodium hydroxide in dropwise fashion. After stirring at rt for 1 hour, the reaction was cooled to 0C and was acidified to pH2-3. Diethyl ether was added and the product was extracted into the organic phase. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to afford 5.1 g (71%) of the titled compound as a white solid.

IS-MS, m/e 440 (m + 1).

**Intermediate PAA-23**

**N-Boc-N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)glycine.**

To a solution of N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)glycine (1.0 g, 3.2 mmol, 1 equiv) in 6 mL of acetone and 6 mL of water at rt was added triethylamine (0.97 mL, 7.0 mmol, 2.1 equiv.) followed by addition of BOC-ON (0.76 g, 3.1 mmol, 0.95 equiv). After stirring at rt overnight, the reaction was diluted with water and washed with ether. The aqueous phase was then acidified with 0.5M citric acid and the product was extracted into diethyl ether. The combined organic phases were

washed with brine, dried over sodium sulfate, filtered, and concentrated to afford 0.38 g (29%) of the titled compound as a crude yellow oil.

IS-MS, m/e 408 (m +1).

**General Experimental Procedures: Synthesis of Inhibitors**

**Coupling Method A:**

The coupling of an amine and carboxylic acid to form an amide. A solution of the amine (1 equiv) and carboxylic acid (1.1 equiv) in a suitable solvent (DMF, and/or methylene chloride) was treated with diethyl cyanophosphonate (1.1 equiv) followed by addition of triethylamine or diisopropylethyl amine (0 to 3 equiv) to the mixture. After completion of the reaction by thin-layer chromatography, the mixture was partitioned between a suitable solvent (EtOAc, and/or methylene chloride) and washed with 1N NaOH, water, brine, and concentrated. The crude mixture was then purified, as indicated, or used directly in subsequent transformations.

**Coupling Method B:**

The coupling of an amine and carboxylic acid to form an amide. A solution of the amine (1 equiv) and carboxylic acid (1.1 equiv) in a suitable solvent (DMF, and/or methylene chloride) was treated with a carbodiimide-based dehydrating agent (e.g. DCC, or EDCI)(1.0 equiv). In general, addition of a benzotriazole-based reagent (e.g. HOBT, or HOAT)(1 equiv) improved reaction yields. After completion of the reaction by thin-layer chromatography, the mixture was partitioned between a suitable solvent (EtOAc, and/or methylene chloride) and washed with 1N NaOH, water, brine, and concentrated. The crude mixture was then purified, as indicated, or used directly in subsequent transformations.

**Coupling Method C:**

The coupling of an amine and acid chloride to form an amide. A solution of the amine (1 equiv) in an appropiate solvent

(chloroform, and/or methylene chloride) and pyridine (1-10 equiv) was treated with an acid chloride (1.1 equiv). After completion of the reaction by thin-layer chromatography, the mixture was partitioned between a suitable solvent (EtOAc, methylene chloride, and/or chloroform) and washed with 1N NaOH, water, brine, and concentrated. The crude mixture was then purified, as indicated, or used directly in subsequent transformations.

**Deprotection Method A:**

A mixture of 10% Palladium on carbon and the starting material in an appropriate solvent (EtOAc, EtOH, and/or HOAc) was placed under an atmosphere of hydrogen. Upon completion, the mixture was filtered and the resulting filtrate concentrated. The crude mixture was then purified, as indicated, or used directly in subsequent transformations.

**Alkylation Method A:**

A solution of the starting material (1 equiv) in 5-10% HOAc in methanol (anhydrous) was treated with the indicated aldehyde or ketone (2-10 equiv) followed by sodium cyanoborohydride (2-10 equiv). After completion, the mixture was concentrated and the residue was either partitioned between a suitable solvent (EtOAc, methylene chloride, and/or chloroform) and washed with 1N NaOH, water, brine, and concentrated or directly loaded onto an ion-exchange resin (SCX, Varian) and eluted with methanol followed by 2N ammonia in methanol. Concentration of the later fractions afforded the free base product. The crude mixture was then purified, as indicated, or used directly in subsequent transformations.

**Preparation of Starting Materials**

**1-(Benzyloxycarbonyl-D-phenylglycinyl)piperidine-4-methanol (Coupling Method A):** A solution of benzyloxycarbonyl-D-phenylglycine (5.0 g, 17.5 mmol) and 4-piperidinemethanol (1.83 g, 15.9 mmol) in 90 mL of methylene chloride was cooled

in a methanol/ice bath and then treated with diethyl cyanophosphonate (2.67 mL, 17.5 mmol) followed by ethyl diisopropylamine (3.1 mL). After 5 h, the mixture was concentrated, diluted with EtOAc and saturated aqueous potassium carbonate, and the resulting layers separated. The organic layer was washed (with aqueous potassium carbonate, 1 N HCl, brine), dried over magnesium sulfate, filtered, concentrated, and the residue purified by column chromatography ($SiO_2$: 70%-80% EtOAc:hexane), affording 1.54 g (25%) of the title compound.

$^1$NMR

IS-MS, m/e 725 (M + 1).

Analysis for $C_{22}H_{26}N_2O_4 \cdot 0.15\ H_2O$:

Calcd: C, 68.6; H, 6.9; N, 7.3;

Found: C, 68.5; H, 6.9; N, 7.1.

**1-(D-Phenylglycinyl)piperidine-4-methanol**

Using Deprotection Method A, 1-(benzyloxycarbonyl-D-phenylglycinyl)piperidine-4-methanol (3.93 g, 29.5 mmol) and 10% palladium on carbon (1.30 g) in 2:1 EtOAc:EtOH (75 mL) afforded 2.31 g (88%) of the title compound.

$^1$NMR

IS-MS, m/e 249 (M+1).

**Preparation of Intermediates A-1 - A-3**

**Intermediate A-1**

**1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-methanol.**

Using Coupling Method C, 1-(D-phenylglycinyl)piperidine-4-methanol (1.23 g, 4.96 mmol) and p-anisoyl chloride (0.888 g, 5.21 mmol) afforded, after purification by column chromatography ($SiO_2$: 1:1 to 1:9 hexanes:EtOAc), 1.26 g (66%) of the title compound.

$^1$NMR

IS-MS, m/e 383 (M+1).

**Intermediate A-2**

**1-(Indole-6-carbonyl-D-phenylglycinyl)piperidine-4-methanol.**

**(Coupling Method B):** A solution of 1-(D-phenylglycinyl) piperidine-4-methanol (500 mg, 2.02 mmol), indole-6-carboxylic acid (325 mg, 2.02 mmol), and 1-hydroxy-7-azabenzotriazole (275 mg, 2.02 mmol) in 10 mL of DMF was treated with DCC (415 mg, 2.02 mmol). After 15 h, the mixture was concentrated and the residue dissolved in EtOAc. The organic layer was washed (with 2 N NaOH, water, brine), dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography ($SiO_2$: EtOAc), affording 780 mg (98%) of the title compound.

$^1$NMR

IS-MS, m/e 383 (M + 1).

**Intermediate A-3**

**1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)piperidine-4-methanol.**

Using Coupling Method B, 1-(D-phenylglycinyl)piperidine-4-methanol (9.90 g, 39.9 mmol) and 3-chloroindole-6-carboxylic acid (8.56 g, 43.9 mmol) afforded, after purification by column chromatography ($SiO_2$: 95% EtOAc in hexane), 8.95 g (53%) of the title compound.

$^1$NMR

IS-MS, m/e 426 (M + 1).

**Preparation of Intermediate B-1**

**Intermediate B-1**

**1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde**

A solution of 1-(4-methoxybenzoyl-D-phenylglycinyl)piperidine-4-methanol (0.800 g, 2.08 mmol) and N-methylmorpholine oxide (0.366 g, 3.13 mmol) in methylene chloride (15 mL) was treated with tetrapropylammonium perruthenate (TPAP, 2 mg). After 14 h, the mixture was treated with additional TPAP (5 mg). After

20 h, the mixture was treated with additional TPAP (5 mg). After 32 h, the mixture was loaded directly onto a column and purified by column chromatography ($SiO_2$: 1:1 to 1:4 hexanes:EtOAc) affording 0.286 g (36%) of the title compound.
$^1$NMR
IS-MS, m/e 381 (M+1).

**Preparation of Intermediates C-2 - C-3**

**Intermediate C-2**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-(methylsulfonyl-oxymethyl)piperidine.**

A solution of 1-(indole-6-carbonyl-D-phenylglycinyl)-piperidine-4-methanol (2.82 g, 7.21 mmol) and triethylamine (2.0 mL) in 40 mL of methylene chloride was treated with methanesulfonyl chloride (1.1 mL, 14.0 mmol). After 2 h, mixture was concentrated and the residue purified by column chromatography ($SiO_2$: 90% EtOAc in hexane) to afford 2.80 g (83%) of the title compound.
$^1$NMR
IS-MS, m/e 470 (M + 1).

**Intermediate C-3**

**1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-(methylsulfonyloxymethyl)piperidine.**

Using a procedure similar to that described above for Intermediate C-2, 1-(3-chloroindole-6-carbonyl-D-phenylglycinyl)piperidine-4-methanol (8.95 g, 21.0 mmol) afforded, after purification by column chromatography ($SiO_2$: 80% to 99% EtOAc in hexane), 2.58 g (24%) of the title compound.
$^1$NMR
IS-MS, m/e 504 (M + 1).

**Preparation of Intermediate D-1**

**4-(Piperidin-1-ylmethyl)piperidine bis-Hydrochloride Salt.**

A solution of 4-(piperidin-1-ylmethyl)pyridine (10.0 g, 0.056 mol; prepared using a similar procedure to that described in US430491) and platinum oxide (1.5 g) in 55 mL of ethanol and 18 mL of 12 N HCl was placed under an atmosphere of hydrogen (4.1 bar, 60 psig). After 15 h, the mixture was filtered, concentrated, and residue triturated with methanol affording 9.0 g of the title compound as a bis hydrochloride salt.
$^1$NMR
IS-MS, m/e 183 (M + 1).

**1-(Benzyloxycarbonyl-D-phenylglycinyl)-4-[(piperidin-1-yl)-methyl]piperidine.**

Using Coupling Method A, benzyloxycarbonyl-D-phenylglycine (17.1 g, 60.1 mmol) and 4-(piperidin-1-ylmethyl)piperidine (10.0 g, 54.6 mmol) afforded, after purification by column chromatography ($SiO_2$: 2% to 3% [2 N ammonia in methanol]:methylene chloride) 10.7 g (43%) of the title compound.
$^1$NMR
IS-MS, m/e 451 (M + 1).
Analysis for $C_{27}H_{35}N_3O_3$:
Calcd: C, 72.1; H, 7.8; N, 9.3;
Found: C, 72.0; H, 7.7; N, 9.4.

**Intermediate D-1.**

**1-(D-Phenylglycinyl)-4-[(piperidin-1-yl)methyl]piperidine.**

Using Deprotection Method A, 1-(benzyloxycarbonyl-D-phenylglycinyl)-4-[(piperidin-1-yl)methyl]piperidine (10.7 g, 23.8 mmol) and 10% palladium on carbon (1.35 g) in 200 mL of 1:1 EtOH:EtOAc afforded the title compound.
$^1$NMR
IS-MS, m/e 315 (M + 1).

**Preparation of Examples 1-5**

**General Procedure:** Unless otherwise indicated, the product of

Examples 1-5 was obtained from the indicated amine and 1-(4-methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (Intermediate B-1) using Alkylation Method A.

**Example 1.**

**1-[(4-Methoxybenzoyl-D-phenylglycinyl)]-4-[(isopropylamino)-methyl]piperidine hydrochloride**

1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and isopropylamine afforded, after treatment of the isolated product with excess hydrochloric acid in methanol and concentration, 37 mg of the title compound as a hydrochloride salt.

$^1$NMR

IS-MS, m/e 424 (M+1)

**Example 2.**

**1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-[(dimethylamino)-methyl]piperidine**

1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and dimethylamine afforded 25 mg (47%) of the title compound.

$^1$NMR

IS-MS, m/e 410 (M+1)

**Example 3.**

**1-[(4-Methoxybenzoyl-D-phenylglycinyl)]-4-[(N,N-diethyl-amino)methyl]piperidine hydrochloride**

1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and diethylamine afforded, after treatment of isolated product with excess hydrochloric acid in methanol and concentration, 42 mg of the title compound as a hydrochloride salt.

$^1$NMR

IS-MS, m/e 438 (M+1)

**Example 4.**

**1-[(4-Methoxybenzoyl-D-phenylglycinyl)]-4-[(1-pyrrolidinyl)-methyl]piperidine**

1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and pyrrolidine afforded 27 mg (47%) of the title compound.

$^1$NMR

IS-MS, m/e 436 (M+1)

**Example 5.**

**1-[(4-Methoxybenzoyl-D-phenylglycinyl)]-4-[(3-pyrrolin-1-yl)-methyl]piperidine hydrochloride**

1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and 3-pyrroline afforded, after treatment of isolated product with excess hydrochloric acid in methanol and concentration, 43 mg of the title compound as a hydrochloride salt.

$^1$NMR

IS-MS, m/e 434 (M+1)

**Preparation of Examples 6-18**

**General Procedure:** Unless otherwise indicated, the product of Examples 6-18 was obtained from the indicated amine and 1-(indole-6-carbonyl-D-phenylglycinyl)-4-(methylsulfonyl-oxymethyl)piperidine (Intermediate C-2) or 1-(3-chloroindole-6-carbonyl-D-phenylglycinyl)-4-(methylsulfonyloxy-methyl)piperidine (Intermediate C-3) using a procedure similar to that described in Example 6.

**Example 6.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(isopropylamino)-methyl]piperidine Trifluoroacetate Salt.**

A solution of 1-(indole-6-carbonyl-D-phenylglycinyl)-4-(methylsulfonyloxymethyl)piperidine (100 mg, 0.213 mmol) and isopropylamine (0.18 mL, 2.1 mmol) in 1 mL of THF was treated

with potassium carbonate (60 mg) and sodium iodide (32 mg, 0.21 mmol), and the mixture was heated at reflux. After 16 h, the mixture was concentrated and the residue purified by rpHPLC chromatography affording 24 mg (21%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 433 (M + 1).

**Example 7.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[4-(pyrrolidin-1-yl)methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (200 mg, 0.426 mmol) and pyrrolidine (0.85 mmol) afforded, after purification by rpHPLC chromatography, 38 mg (16%) of the title compound as a trifluoroacetate salt.

$^1$NMR

**Example 8.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(diethylamino)-methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and diethylamine (2.1 mmol) afforded, after purification by rpHPLC chromatography, 59 mg (49%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 447 (M + 1).

**Example 9.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(piperidin-1-yl)-methyl)piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and piperidine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 16 mg (13%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 459 (M + 1).

**Example 10.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(4-hydroxypiperidin-**

**1-yl)methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and 4-hydroxypiperidine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 32 mg (25%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 475 (M + 1).

**Example 11.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(piperazin-1-yl)-methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and piperazine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 85 mg (70%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 460 (M + 1).

**Example 12.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(4-methylpiperazin-1-yl)methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and 1-methylpiperizine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 66 mg (53%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 474 (M + 1).

**Example 13.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(3-hydroxy-pyrrolidin-1-yl)methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and 3-hydroxypyrrolidine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 36 mg (30%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 461 (M + 1).

**Example 14.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(R)-(3-hydroxymethylpyrrolidin-1-yl)methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and (R)-3-hydroxymethylpyrrolidine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 32 mg (26%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 475 (M + 1).

**Example 15.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(S)-(3-hydroxymethylpyrrolidin-1-yl)methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and (S)-3-hydroxymethylpyrrolidine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 36 mg (29%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 475 (M + 1).

**Example 16.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(4-hydroxymethylpiperidin-1-yl)methyl]piperidine Trifluoroacetate Salt.**

Intermediate C-2 (100 mg, 0.213 mmol) and 4-hydroxymethylpiperidine (2.3 mmol) afforded, after purification by rpHPLC chromatography, 28 mg (22%) of the title compound as a trifluoroacetate salt.

$^1$NMR

IS-MS, m/e 489 (M + 1).

**Example 17.**

**1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-[(piperidin-1-yl)methyl]piperidine Hydrochloride Salt.**

Intermediate C-3 (1.0 g, 2.0 mmol) and piperidine (6.0 mmol) afforded, after purification by column chromatography ($SiO_2$:

2% to 4% [2 N ammonia in methanol]:methylene chloride) and salt formation with hydrochloric acid, 443 mg (41%) of the title compound as a hydrochloride salt.

$^1$NMR

IS-MS, m/e 493 (M + 1).

**Example 18.**

**1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-[(3-hydroxypiperidin-1-yl)methyl]piperidine.**

Intermediate C-3 (1.50 g, 3.0 mmol) and 3-hydroxypiperidine (9.0 mmol) afforded, after purification by column chromatography ($SiO_2$: 2% to 3% [2 N ammonia in methanol]:methylene chloride), 1.10 g of the title compound.

$^1$NMR

IS-MS, m/e 507 (M + 1).

**Preparation of Examples 19-21**

**General Procedure:** Unless otherwise indicated, the product of Examples 19-21 was obtained from the indicated carboxylic acid and 1-(D-phenylglycinyl)-4-[(piperidin-1-yl)methyl]piperidine (Intermediate D-1) using a procedure similar to that described in Example 19.

**Example 19.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[(piperidin-1-yl)-methyl]piperidine.**

**(Coupling Method B):** A solution of 1-(D-phenylglycinyl)-4-[(piperidin-1-yl)methyl]piperidine (4.00 g, 12.7 mmol) and indole-6-carboxylic acid (2.25 g, 13.9 mmol) in 60 mL of DMF was treated with HOBT (1.88 g, 13.9 mmol), the mixture cooled to 0 °C, and then treated with DCC (2.87 g, 13.9 mmol). After 15 h, the mixture was diluted with EtOAc, filtered, and the filtrate concentrated. The residue was purified by column chromatography ($SiO_2$; 2% to 3.5% [2 N ammonia in methanol]:methylene chloride) to afford 3.1 g (53%) of the title compound.

$^1$NMR

IS-MS, m/e 459 (M + 1).

**Example 20.**

**1-(3-Methylindole-6-carbonyl-D-phenylglycinyl)-4-[(piperidin-1-yl)methyl]piperidine Hydrochloride Salt.**

Intermediate D-1 (2.00 g, 6.35 mmol) and 3-methylindole-6-carboxylic acid (1.22 g, 6.98 mmol) afforded, after formation of the hydrochloride salt, 1.29 g (41%) of the title compound.

$^1$NMR

IS-MS, m/e 473 (M + 1).

Analysis for $C_{29}H_{36}N_4O_2 \cdot HCl \cdot 0.75\ H_2O$:

Calcd: C, 66.7; H, 7.4; N, 10.7;

Found: C, 66.7; H, 7.2; N, 10.8.

**Example 21.**

**1-(5-Chloroindole-2-carbonyl-D-phenylglycinyl)-4-[(piperidin-1-yl)methyl]piperidine Hydrochloride Salt.**

Intermediate D-1 and 5-chloro-1H-indole-2-carboxylic acid (1.36 g, 6.98 mmol) afforded, after formation of the hydrochloride salt, 1.52 g (45%) of the title compound.

$^1$NMR

IS-MS, m/e 493 (M + 1).

Analysis for $C_{28}H_{33}ClN_4O_2 \cdot HCl \cdot 0.75\ H_2O$:

Calcd: C, 61.9; H, 6.6; N, 10.3;

Found: C, 61.8; H, 6.4; N, 10.4.

The following compounds are prepared using similar procedures to those described above and the requisite starting materials:

**1-[Indole-6-carbonyl-D,L-(2-methoxyphenyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine**

**1-[Indole-6-carbonyl-D,L-(5-thiazoyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine**

1-[Indole-6-carbonyl-D,L-(2-aminothiazol-4-yl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[Indole-6-carbonyl-D,L-(2-methylthiazol-4-yl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Methylindole-6-carbonyl-D,L-(4-pyridyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Chloroindole-6-carbonyl-D,L-(4-pyridyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[Indole-6-carbonyl-D,L-(2-methoxyphenyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Methylindole-6-carbonyl-D,L-(2-methoxyphenyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Chloroindole-6-carbonyl-D,L-(2-methoxyphenyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[Indole-6-carbonyl-D,L-(1-naphthyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Methylindole-6-carbonyl-D,L-(1-naphthyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Chloroindole-6-carbonyl-D,L-(1-naphthyl)glycinyl]-4-[(piperidin-1-yl)methyl]pip ridine

1-[Indole-6-carbonyl-D,L-(2-chlorophenyl)glycinyl]-4-

[(piperidin-1-yl)methyl]piperidine

1-[3-Methylindole-6-carbonyl-D,L-(2-chlorophenyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Chloroindole-6-carbonyl-D,L-(2-chlorophenyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[Indole-6-carbonyl-D,L-(8-quinolinyl)glycinyl]-4-[(piperidin-1-yl)methyl)piperidine

1-[3-Methylindole-6-carbonyl-D,L-(8-quinolinyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Chloroindole-6-carbonyl-D,L-(8-quinolinyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[Indole-6-carbonyl-D,L-(4-quinolinyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Methylindole-6-carbonyl-D,L-(4-quinolinyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

1-[3-Chloroindole-6-carbonyl-D,L-(4-quinolinyl)glycinyl]-4-[(piperidin-1-yl)methyl]piperidine

**Assay protocols**

Enzyme Inhibition assays:

The ability of a test compound to inhibit factor Xa may be evaluated in one or more of the following Enzyme Inhibition

assays, or in other standard assays known to those skilled in the art.

Enzyme Inhibition Assay 1

Enzyme assays were carried out at room temperature in 0.1M phosphate buffer, pH7.4 according to the method of Tapparelli et al (J. Biol. Chem. 1993,268,4734-4741). Purified human factor Xa, trypsin, thrombin and plasmin were purchased from Alexis Corporation, Nottingham, UK. Urokinase was purchased from Calbiochem, Nottingham, UK. Chromogenic substrates for these enzymes; pefachrome-FXA, pefachrome-TRY, pefachrome-TH, pefachrome-PL and pefachrome-UK were purchased from Pentapharm AG, Basel, Switzerland. Product (*p*-nitroaniline) was quantified by adsorption at 405nm in 96 well microplates using a Dynatech MR5000 reader (Dynex Ltd, Billingshurst, UK). Km and Ki were calculated using SAS PROC NLIN (SAS Institute, Cary, NC, USA, Release 6.11) $K_m$ values were determined as 100.9μM for factor Xa/pefachrome-FXA and 81.6μM for trypsin/pefachrome-TRY. Inhibitor stock solutions were prepared at 40mM in Me2SO and tested at 500μM, 50μM and 5μM. Accuracy of Ki measurements was confirmed by comparison with Ki values of known inhibitors of factor Xa and trypsin.

In agreement with published data, benzamidine inhibited factor Xa, trypsin, thrombin, plasmin and urokinase with Ki values of 155μM, 21μM, 330nM, 200nM and 100nM respectively. NAPAP inhibited thrombin with a Ki value of 3nM. Compounds of the invention were found to have activity in these assays.

Enzyme Inhibition Assay 2

Human factor Xa and human thrombin were purchased from Enzyme Research Laboratories (South Bend, Indiana, USA). Other proteases were from other commercial sources. Chromogenic para-nitroanilide peptide protease substrates were purchased from Midwest Biotech (Fishers, Indiana, USA).

The binding affinities for human factor Xa were measured as apparent association constants (Kass) derived from protease inhibition kinetics as described previously.[a,b,c,d] The apparent Kass values were obtained using automated (BioMek-1000) dilutions of inhibitors (Kass determinations are performed in triplicate at each of four-eight inhibitor concentrations) into 96-well plates and chromogenic substrate hydrolysis rates determined at 405 nm using a Thermomax plate reader from Molecular Devices (San Francisco). For factor Xa inhibition, the assay protocol was: 50 µl buffer (0.06 M tris, 0.3 M NaCl, pH 7.4); 25 µl inhibitor test solution (in MeOH); 25 µl human factor Xa (32 nM in 0.03 M tris, 0.15 M NaCl, 1 mg/ml HSA); finally, 150 µl BzIleGluGlyArgpNA (0.3 mM in water) added within 2 min to start hydrolysis. Final factor Xa was 3.2 nM. Free [Xa] and bound [Xa] were determined from linear standard curves on the same plate by use of SoftmaxPro software for each inhibitor concentration and apparent Kass calculated for each inhibitor concentration which produced hydrolysis inhibition between 20% and 80% of the control (3.2 nM factor Xa): apparent Kass $= [E:I]/[E_f][I_f] = [E_b]/[E_f][I^o-I_b]$. The apparent Kass values so obtained are approximately the inverse of the Ki for the respective inhibitors [1/appKass = app Ki]. The variability of mean apparent Kass values determined at the single substrate concentration was +/- 15%. The assay system Km was measured as 0.347 +/- 0.031 mM [n=4]; and Vmax was 13.11 +/- 0.76 µM/min.

Kass values were determined with thrombin and other proteases using the same protocol with the following enzyme and substrate concentrations: thrombin 5.9 nM with 0.2 mM BzPheValArgpNA; XIa 1.2 nM with 0.4 mM pyroGluProArgpNA; XIIa 10 nM with 0.2 mM HDProPheArgpNA; plasmin 3.4 nM with 0.5 mM HDValLeuLyspNA; nt-PA 1.2 nM with 0.8 mM HDIleProArgpNA; and

urokinase 0.4 nM with 0.4 mM pyroGluGlyArgpNA; aPC 3 nM with 0.174 mM pyroGluProArgpNA; plasma kallikrein 1.9 nM with D-ProPheArgpNA; bovine trypsin 1.4 nM with 0.18 mM BzPheValArgpNA.

Citations

(a) Sall DJ, JA Bastian, SL Briggs, JA Buben, NY Chirgadze, DK Clawson, ML Denny, DD Giera, DS Gifford-Moore, RW Harper, KL Hauser, VJ Klimkowski, TJ Kohn, H-S Lin, JR McCowan, AD Palkowitz, GF Smith, ME Richett, K Takeuchi, KJ Thrasher, JM Tinsley, BG Utterback, S-CB Yan, M Zhang. Dibasic Benzo[b]thiophenes Derivatives as a Novel Class of Active Site Directed Thrombin Inhibitors. 1. Determination of the Serine Protease Selectivity, Structure-Activity Relationships and Binding Orientation. J Med Chem 40 3489-3493 (1997).

(b) Smith GF, TJ Craft, DS Gifford-Moore, WJ Coffman, KD Kurz, E Roberts, RT Shuman, GE Sandusky, ND Jones, N Chirgadze, and CV Jackson. A Family of Arginal Thrombin Inhibitors Related to Efegatran. Sem. Thrombos. Hemost. 22, 173-183 (1996).

(c) Smith GF, DS Gifford-Moore, TJ Craft, N Chirgadze, KJ Ruterbories, TD Lindstrom, JH Satterwhite. Efegatran: A New Cardiovascular Anticoagulant. In New Anticoagulants for the Cardiovascular Patient. Ed. R Pifarre. Hanley & Belfus, Inc., Philadelphia (1997) pp 265-300.

(d) Sall DJ, JA Bastian, NY Chirgadze, ML Denny, MJ Fisher, DS Gifford-Moore, RW Harper, VJ Klimkowski, TJ Kohn, HS Lin, JR McCowan, ME Richett, GF Smith, K Takeuchi, JE Toth, M Zhang. Diamino Benzo[b]thiophene Derivatives as a Novel Class of Active Site Directed Thrombin Inhibitors: 5. Potency, Efficacy and

Pharmacokinetic Properties of Modified C-3 Side Chain Derivatives. In press, J Med Chem (1999).

In general, the compounds of formula (I) exemplified herein have been found to exhibit a Ki of 10 μM or less in Assay 1 and/or a Kass of at least 0.1 x $10^6$ L/mole in Assay 2.

The ability of a test compound to elongate Partial Thromboplastin Time (Prothrombin Time) may be evaluated in the following test protocols.

Partial Thromboplastin Time (Prothrombin) Test Protocol

Venous blood was collected into 3.2% (0.109m) trisodium citrate vacutainer tubes at 1 volume of anticoagulant to nine volumes of blood. The blood cells were separated by centrifugation at 700g for ten minutes to yield plasma, which was frozen at 70°C until required.

To perform the test, 100μl of plasma was pipetted into in a glass test tube, 1μl of test compound in DMSO was added, and allowed to warm to 37° over two minutes. 100μl of warm (37°) Manchester (tissue thromboplasin) reagent (Helena Biosciences, UK) was added, allowed to equilibrate for two minutes. 100μl of warm (37°) 25mM calcium chloride solution was added to initiate clotting. The test tube was tilted three times through a 90° angle every five seconds to mix the reagents and the time to clot formation recorded. Data from a series of observations and test compound concentrations are analysed by a SAS statistical analysis program and a CT2 (Concentration required to double clotting time) for each compound is generated.

Compounds of the invention were found to significantly elongate the partial thromboplastin time (Prothrombin time).

Alternative Prothrombin Time and APTT Protocols

Coagulation Determinations. Prothrombin Times and APTT values were determined in HUMAN PLASMA with a STA instrument (Stago). BioPT is a special non-plasma clotting assay triggered with human tissue factor (Innovin). Possible binding to albumen or to lipid was assessed by comparing the BioPT effects in the presence/absence of 30 mg/ml human albumen (HSA) and 1 mg/ml phosphatidyl choline (PC). Inhibitors were delivered in 50% MeOH vehicle.

**APTT ASSAY**

75 µl plasma Citrol *Baxter-Dade* Citrated Normal Human Plasma

25 µl test sol'n

75 µl Actin *Baxter-Dade* Activated Cephaloplastin incubate 2 min. @ 37°

75 µl $CaCl_2$ (0.02 M)

**PT ASSAY**

75 µl plasma

25 µl test sol'n

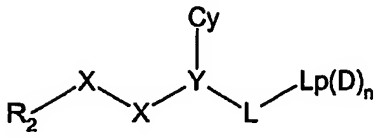
75 µl saline incubate 1 min. @ 37° C

75 µl Innovin *Baxter-Dade* Recombinant Human Tissue Factor

Compounds of the invention were found to be potent inhibitors of factor Xa.

Claims

1. A serine protease inhibitor compound of formula (I)




(I)

wherein:

$R_2$ is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or $R_1$, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or $R_{1j}$, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that $R_2$ cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, $CR_{1a}$, $C(R_{1a})_2$ or $NR_{1a}$ group, at least one X being C, CO, $CR_{1a}$ or $C(R_{1a})_2$;

each $R_{1a}$ independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

$R_1$ is as defined for $R_{1a}$, provided that $R_1$ is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a $CR_{1b}$ group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups $R_{3a}$ or phenyl

optionally substituted by $R_{3a}$ or $R_{3i}X_i$;

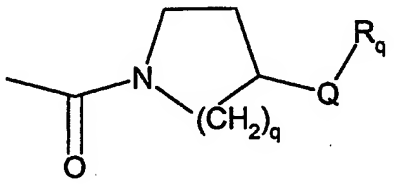
each $R_{3a}$ independently is $R_{1c}$, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein $X^3$ is O or S; and $R^{11}$ and $R^{12}$ are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

$X_i$ is a bond, O, NH or $CH_2$;

$R_{3i}$ is phenyl, pyridyl or pyrimidinyl optionally substituted by $R_{3a}$;

$R_{1b}$, $R_{1c}$ and $R_{1j}$ are as defined for $R_{1a}$; and

$-L-Lp(D)_n$ is



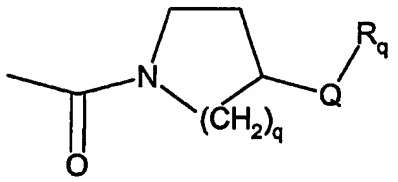

q is 1 or 2;

Q is methylene; and $R_q$ is $NR_aR_b$ in which each of $R_a$ and $R_b$ independently is hydrogen or $C_{1-3}$alkyl; or one of $R_a$ and $R_b$ is hydrogen or methyl and the other of $R_a$ and $R_b$ is (3-6C)cycloalkyl, pyrid-4-yl, $-CH_2-R_c$ or $-CH_2-R_d$ in which $R_c$ is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, $SO_2NH_2$, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which $R_d$ is isopropyl or cyclopentyl, or $NR_aR_b$ is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino may be optionally substituted on a ring carbon atom by hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy,

methoxycarbonyl or ethoxycarbonyl (provided that the amino, hydroxy or alkoxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring oxygen, sulfur or nitrogen atom) and in which the piperazino or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position];
or a physiologically-tolerable salt thereof.

2. A compound according to claim 1 wherein the azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or tetrahydro-1,4-diazepino in $NR_aR_b$ is optionally substituted on a ring carbon atom by methyl, hydroxy or hydroxymethyl.

3. A compound according to claim 1 wherein -L-Lp$(D)_n$ is of the formula:

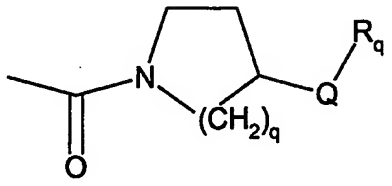



wherein:
q is 1 or 2;
Q is methylene; and $R_q$ is $NR_aR_b$ in which each of $R_a$ and $R_b$ independently is hydrogen or $C_{1-3}$alkyl; or one of $R_a$ and $R_b$ is hydrogen or methyl and the other of $R_a$ and $R_b$ is $-CH_2-R_c$ or $-CH_2-R_d$ in which $R_c$ is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, $SO_2NH_2$, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which $R_d$ is isopropyl or cyclopentyl, or $NR_aR_b$ is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino may be a 3,4-didehydro deriviative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position;
or a physiologically-tolerable salt thereof.

4. A compound according to any of claims 1 to 3 wherein q is

2.

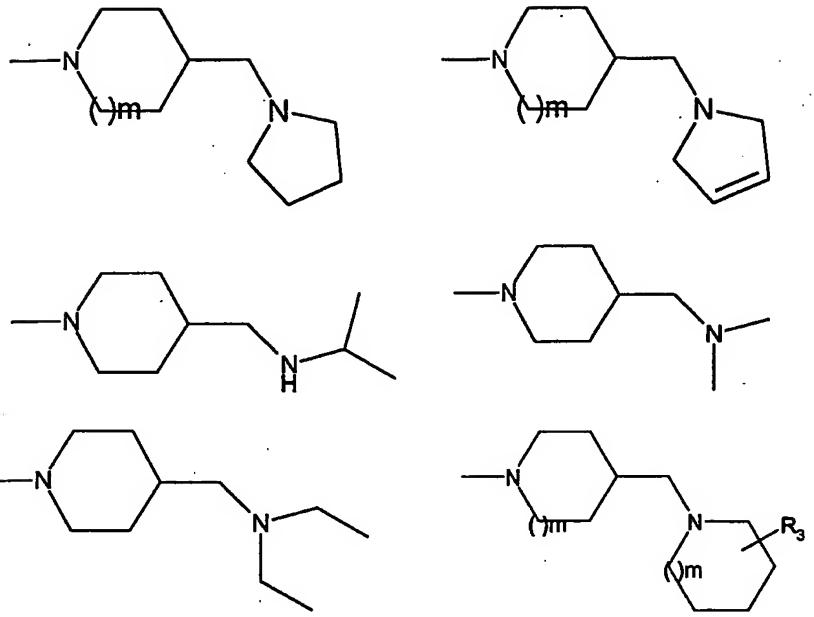
5. A compound according to any of claims 1 to 4 wherein -L-Lp(D)$_n$ is of the formula:




wherein:
q is 1 or 2;
Q is methylene; and $R_q$ is $NR_aR_b$ in which each of $R_a$ and $R_b$ independently is hydrogen or $C_{1-3}$alkyl; or one of $R_a$ and $R_b$ is hydrogen and the other is (3-6C)cycloalkyl or pyrid-4-yl; or $NR_aR_b$ is azetidino, pyrrolidino, piperidino or piperazino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino, pyrrolidino, piperidino or piperazino may be optionally substituted on a ring carbon atom by methyl, hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

6. A compound according to claim 5 wherein:
$R_q$ is $NR_aR_b$ in which $R_a$ is hydrogen or $C_{1-3}$alkyl and $R_b$ is $C_{1-3}$alkyl; or $R_a$ is hydrogen and $R_b$ is (3-6C)cycloalkyl or pyrid-4-yl; or $NR_aR_b$ is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino [in which a pyrrolidino, piperidino or piperazino may be optionally substituted on a ring carbon atom by hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

7. A compound according to any one of claims 1 to 4 wherein -Lp(D)n is selected from the following formulae:

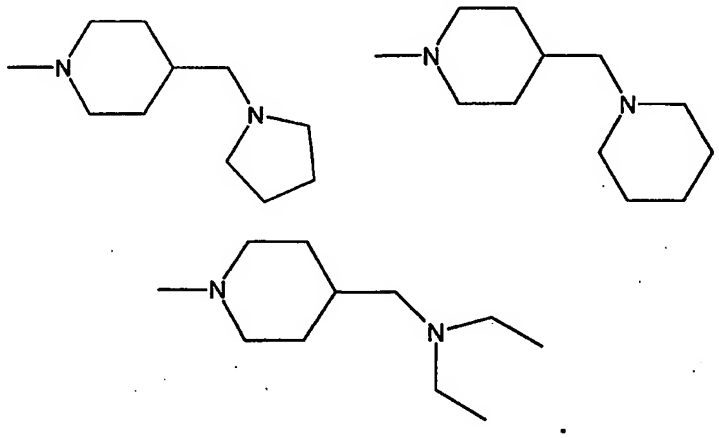


wherein:

m represents 0 or 1;

and when $R_3$ is present as a substituent on a saturated ring, it is selected from hydrogen, hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl and ethoxycarbonyl.

8. A compound according to any of claims 1 to 4 wherein -Lp(D)n is selected from the following formulae:



9. A compound according to any of claims 1 to 5 wherein Rq is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-

hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and 4-methylpiperazino.

10. A compound according to any of claims 1 to 5 wherein Rq is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, 3(S)-hydroxypyrrolidino, 3(S)-hydroxymethylpyrrolidino, 3(R)-hydroxymethylpyrrolidino, piperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, 3-hydroxypiperidino, piperazino and 4-methylpiperazino.

11. A compound according to any one of claims 1 to 10 wherein the 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, in $R_2$, is selected from phenyl, pyrrolyl, pyridyl, pyrazinyl, furyl and thienyl (optionally substituted as defined in claim 1).

12. A compound according to any one of claims 1 to 11 wherein $R_2$ is phenyl (optionally substituted as defined in claim 1).

13. A compound according to any one of claims 1 to 12 wherein $R_2$ is naphthyl, benzimidazolyl, isoquinolinyl, indolyl, indazolyl, 3,4-methylenedioxyphenyl, dihydroindolyl, benzothiazolyl, benzo[b]thiophenyl, benzofuryl, imidazo[1,2-a]pyrimidinyl, tetrahydroimidazo[1,2-a]pyrimidinyl or benzisoxazolyl (each of which is optionally substituted as defined in claim 1).

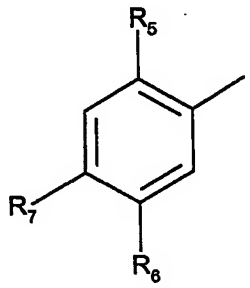
14. A compound according to any one of claims 1 to 13 wherein $R_2$ is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

15. A compound according to any one of claims 1 to 14 wherein optional substituents for $R_2$ are selected from:
fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano,

trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido ($CONH_2$), aminomethyl, methoxy and ethoxy.

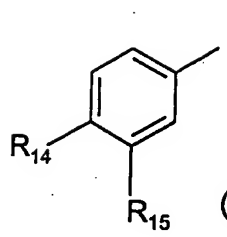
16. A compound according to any one of claims 1 to 15 wherein $R_2$ is optionally substituted by 1 or 2 substituents selected from fluoro, chloro, amino, methyl, ethyl and methoxy.

17. A compound according to any one of claims 1 to 10 wherein $R_2$ is of the formula:

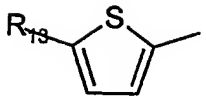



in which $R_5$ is amino, hydroxy or hydrogen, and $R_6$ and $R_7$, which may be the same or different, are halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or $R_1$ (as defined in claim 1) or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered heterocyclic ring, which may itself be substituted by $R_{1j}$ (as defined in claim 1), amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl or haloalkoxy.

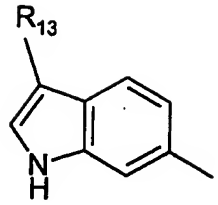
18. A compound according to any one of claims 1 to 10 wherein $R_2$ is selected from one of the formula (A') to (H'):



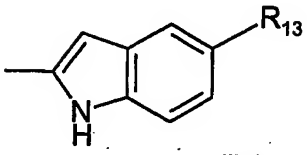

(A')



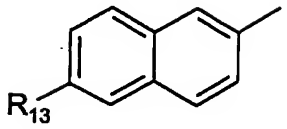

(B')



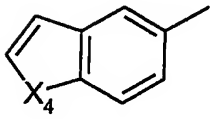

(C')



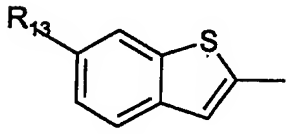

(D')



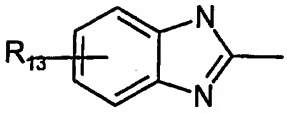

(E')




(F')




(G')




(H')

wherein $X_4$ is O or S, $R_{13}$ is selected from hydrogen, chloro or methyl and $R_{14}$ is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and $R_{15}$ is selected from hydrogen, methyl, fluoro, chloro and amino.

19. A compound according to claim 18, wherein $R_2$ is of the formula (A') (wherein $R_{14}$ is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and $R_{15}$ is selected from hydrogen, methyl, fluoro, chloro and amino) or of the formula (B') (wherein $R_{13}$ is chloro) or of the formula (C') (wherein $R_{13}$ is selected from hydrogen, methyl and chloro) or of the formula (D') (wherein $R_{13}$ is selected from hydrogen and chloro) or of the formula (E') (wherein $R_{13}$ is hydrogen) or of the formula (G') (wherein $R_{13}$ is chloro).

20. A compound according to claim 18, wherein $R_2$ is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

21. A compound according to claim 19 wherein $R_2$ is of the formula (A') and $R_{14}$ and $R_{15}$ are as defined in claim 19.

22. A compound according to claim 19 wherein $R_2$ is of the formula (A') and $R_{14}$ is methoxy and $R_{15}$ is hydrogen.

23. A compound according to any one of claims 1 to 22 wherein -X-X- is selected from -CH=CH-, -CONH-, -CONR$_{1a}$-, -NH-CO-, -NH-CH$_2$-, -CH$_2$-NH-, -CH$_2$O-, -OCH$_2$-, -COO-, -OC=O- and -CH$_2$CH$_2$- wherein R1a is as defined in claim 1.

24. A compound according to any one of claims 1 to 22 wherein -X-X- is -CONH-.

25. A compound according to any one of claims 1 to 24 wherein $R_{1b}$ is hydrogen, methyl or hydroxymethyl.

26. A compound according to any one of claims 1 to 24 wherein $R_{1b}$ is hydrogen.

27. A compound according to any one of claims 1 to 26 wherein Y is CH.

28. A compound according to any one of claims 1 to 27 wherein Cy is an optionally $R_{3a}$ substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinoloyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which $X_i$ is a bond, O, NH or $CH_2$ and $R_{3i}$ is phenyl optionally substituted by $R_{3a}$.

29. A compound according to any one of claims 1 to 27

wherein Cy is an optionally $R_{3a}$ substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

30. A compound according to any one of claims 1 to 29 wherein $R_{3a}$ is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein $X^3$ is O or S; and $R^{11}$ and $R^{12}$ are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy.

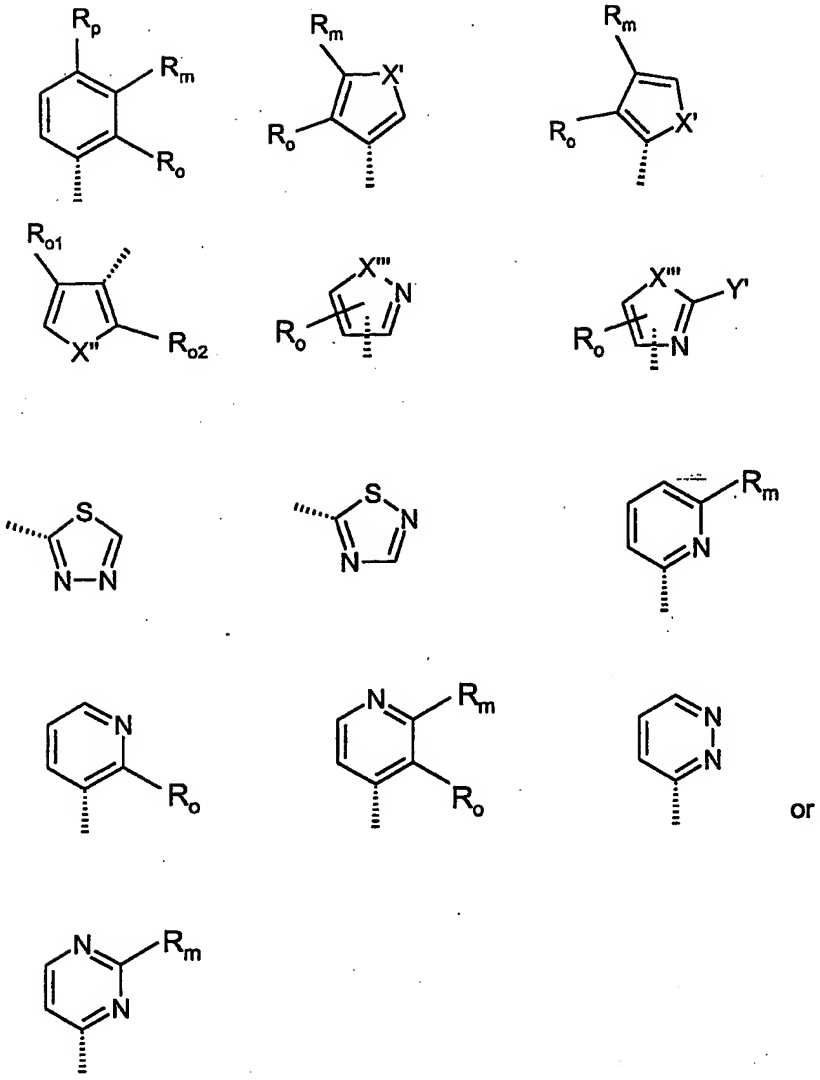
31. A compound according to any one of claims 1 to 27 wherein $R_{3a}$ is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.

32. A compound according to any one of claims 1 to 27 wherein $R_{3a}$ is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl,

methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, $CH_2CONH_2$, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy) and $-C(X^3)N(R^{11})R^{12}$ (wherein $X^3$ is O or S and $R^{11}$ and $R^{12}$ are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group).

33. A compound according to any one of claims 1 to 29 wherein $R_{3a}$ is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, $CH_2CONH_2$, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

34. A compound according to any one of claims 1 to 29 wherein Cy is selected from:



or

wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

$R_o$ is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

$R_m$ is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein $X^3$ is O or S, and $R^{11}$ and $R^{12}$ are

independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);
$R_p$ is selected from hydrogen and fluoro; or
$R_o$ and $R_m$ or $R_m$ and $R_p$ form an -OCH2O- group; or
$R_o$ and $R_m$ together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and
one of $R_{o1}$ and $R_{o2}$ is hydrogen and the other is $R_o$.

35. A compound according to any one of claims 1 to 29 wherein Cy is selected from phenyl (optionally substituted by ethyl, prop-2-yl, phenoxy, hydroxy, ethoxy, benzyloxy, prop-2-yloxy, nitro, amino, acetylamino, methylsufonylamino, dimethylamino, chloro, methoxy, trifluoromethyl, methylthio, methylsulfonyl, tert-butylthio, tert-butylsulfonyl, aminosulfonyl or carbamoyl), pyridyl, thienyl, furanyl, imidazolyl, thiazolyl (optionally substituted by amino or methyl), napththyl, isoquinolinyl and quinolinyl.

36. A compound according to any one of claims 1 to 29 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

37. A compound according to any one of claims 1 to 29 wherein Cy is selected from phenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5yl and quinolin-4-yl.

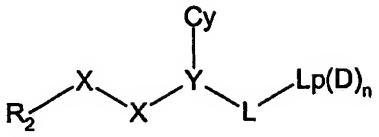
38. A compound according to any one of claims 1 to 29 wherein Cy is phenyl.

39. A compound of the formula:


wherein Cy, $R_2$ and $R_q$ are as defined in claim 1.

# ABSTRACT

Compounds of formula (I)




(I)

in which $R_2$, X, Y, Cy, L and $Lp(D)_n$ have the meanings given in the specification, are inhibitors of the serine protease, factor Xa and are useful in the treatment of cardiovascular disorders.

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J.R.L-T